NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

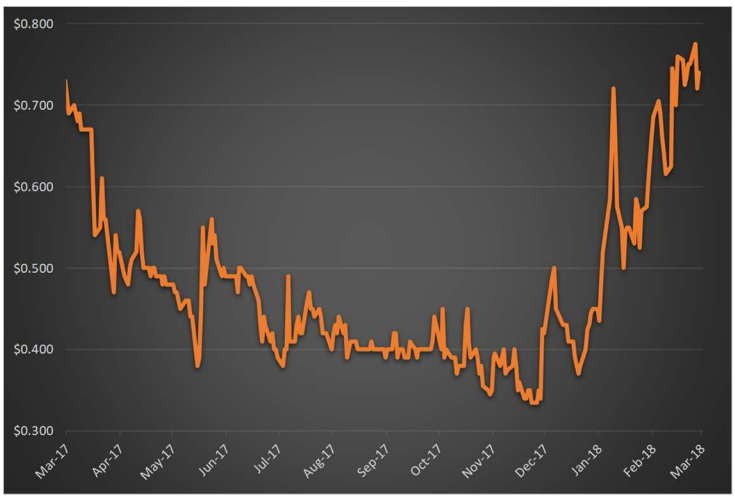
Kazia Therapeutics (ASX: KZA)

Re-Initiation of Coverage – Tuesday 3 April 2018

Picking up where Genentech left off

Glioblastoma is an acute brain cancer with, at the moment, limited treatment options. As such, there's a billion-dollar market opportunity waiting to be realised. That is Kazia Therapeutics' prime focus – and it recently commenced a Phase 2 trial of its small-molecule GDC-0084. Back in 2016, notwithstanding positive Phase 1 results, Genentech offered this candidate for sale and Kazia was the successful bidder, attracted by the prospects for a successful inhibitor of the cellular signalling pathway PI3K. There are others chasing this pathway and in 2014 Gilead obtained approval for Zydelig. But unlike their drug, Kazia's candidate is specifically focused on glioblastoma and has the advantage of a molecule that not only has an already-demonstrated Phase 1 safety record but, uniquely, has the ability to cross the blood-brain barrier. If the recently initiated Phase 2 is successful, there may be accelerated approval for GDC-0084 given the paucity of current glioblastoma treatments. In addition to GDC-0084, Kazia has an ovarian cancer drug (developed internally) that completes Phase 1 in 2018. Kazia was formerly known as Novogen. The name change in late 2017 reflects the new lead compound and the arrival of a highly-experienced management team, led by Dr James Garner. We value Kazia at $0.73 per share base case and $3.50 per share optimistic case. Our target price of $2.10 per share sits at the midpoint of our valuation range. We see Kazia being re-rated by the progress into the clinic of GDC-0084. This note is our original note on Novogen from 7 November 2017, updated for what has happened since then.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.75	$2.10



Stock details

Daily Turnover: ~A$32,000
Market Cap: A$36.3m
Shares Issued: 48.4m
52-Week High: $0.80
52-Week Low: $0.34

Analyst: Stuart Roberts
stuart@ndfresearch.com
+61 447 247 909

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NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research, and introduce investors around the world to potential future billion-dollar companies from 'Down Under'.

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Ferry at the end of a rainbow on Sydney Harbour, August 2014

In this report

Introducing Kazia Therapeutics (ASX: KZA, Nasdaq: KZIA)

Kazia Therapeutics is a Sydney-based cancer drug development company, currently focused on small molecules. For close to 20 years the company, as Novogen, had worked on the discovery and development of various small molecules, mainly with a focus on cancer, where the drugs were derivatives of a natural product found in soybeans. The company's candidates had generated meaningful pre-clinical and clinical data up to Phase 2 but had failed to progress to the market. When Dr James Garner became Kazia's CEO in February 2016[1], the new strategy which he put in place for creating shareholder value was to in-license programmes that had reached the clinical stage, move them forward some way to demonstrate their potential value, and then out-license them to larger companies for commercialisation. The first such programme which passed through all of Kazia's screens was GDC-0084, potentially a new glioblastoma drug. This candidate, a Genentech-developed drug for which rights were acquired October 2016, has completed Phase 1. GDC-0084 is now the company's lead candidate, in Phase 2 clinical development, and to reflect this Novogen changed its name to Kazia Therapeutics in late 2017.

What is GDC-0084 and why is it a potentially valuable new drug to treat glioblastoma? GDC-0084 is an inhibitor of a signalling pathway within cells called PI3K, which has been implicated in a variety of cancers. While many drug candidates have been trialled that work via this pathway, GDC-0084 is understood to be the first that can cross the blood-brain barrier, making it useful to treat brain cancers such as glioblastoma. Kazia is now building on Genentech's Phase 1, which generated some indications of efficacy as well as established a reasonable safety profile. Kazia's Phase 2 initiated in March 2018. Some have questioned the value of GDC-0084, arguing that Big Pharma doesn't just hand valuable candidates over to small development companies[2]. However, in our research we have found that such transactions happen frequently, thanks mainly to changed corporate priorities, and in this note we highlight a number of examples, including the notable Puma/Pfizer transaction of 2011. Kazia argues that Genentech remains supportive of the GDC-0084 programme while it transitions to focus more on its late-stage pipeline. We also argue that the prestige of Genentech as the originator raises the reputation of Kazia as inheritor of the drug's mantle.

KAZIA'S LEAD CANDIDATE WAS ORIGINALLY DEVELOPED BY GENENTECH

What other candidates does Kazia have in the works? Kazia is also working on Cantrixil, a 'super-benzopyran' drug currently in a Phase 1 study in platinum-resistant ovarian cancer which is expected to read out data in 2018[3]. The company also received a grant in early 2017 from the Australian Department of Industry Innovation and Science to develop a new form of anti-tropomyosin technology which is intended to provide potential new therapies for cancer. Early work on this program is generating interesting leads.

Why is Kazia capitalised at only A$36.3m/US$27.9m? Novogen attracted considerable investor attention in the 1990s and 2000s on ASX as a promising cancer drug developer. However, that company never developed a successful drug. We believe that the low market capitalisation prior to the name change to Kazia Therapeutics reflects long-running investor fatigue, as well as some selling by key shareholders who had been associated with

[1] This had been announced some months before – see the Novogen market release dated 10 December 2015 and headlined '*Novogen appoints Dr James Garner as Chief Executive Officer*'
[2] See *After a series of PI3k pileups, Genentech offloads a PhII-ready rival for firesale price* by John Carroll, Endpoints News, 31 October 2016.
[3] Kazia believes that Cantrixil is the only Phase 1 trial in ovarian cancer being run in Australia at the moment.

the previous management team. However, we also believe that the new management team led by CEO James Garner, and the recent progress into Phase 2 of GDC-0084, can help overcome some of this negative investor sentiment and continue re-rating Kazia back to a level more appropriate to a mid-stage cancer drug developer. It helps that Kazia stock is traded on two markets, ASX as well as Nasdaq[4], potentially widening the scope of investors that can be reached.

Ten reasons to consider Kazia Therapeutics

1. **Kazia has a promising new glioblastoma drug in GDC-0084.** The drug, which targets multiple forms of the signalling molecule PI3K, is the first PI3K inhibitor that can pass above the blood-brain barrier. GDC-0084 has shown some promise in glioblastoma in Phase 1 and Kazia initiated a Phase 2 in March 2018.
2. **Kazia is an Orphan drug company with a mid-stage clinical asset.** Glioblastoma being a relatively rare cancer, Kazia is now effectively benefiting from the potential high pricing and lower regulatory burden traditionally associated with Orphan drugs. The FDA granted Orphan Drug Designation for GDC-0084 in February 2018. Kazia believes it may be able to go after accelerated approval for the drug in the event of Phase 2 success.
3. **Glioblastoma could be a company maker for Kazia**, with a new drug in this space potentially worth >US$500m in sales on our numbers.
4. **Kazia is a play on PI3K as a cancer target.** The FDA approval in July 2014 of a PI3K inhibitor called Zydelig, from the major pharma company Gilead, and Bayer's gaining of FDA approval in September 2017 for Aliqopa[5], has established that drugs can work which target the PI3K pathway, and will likely attract investors to re-evaluate this class. Kazia is now a participant in the race to find better PI3K inhibitors.

PI3K INHIBITOR DRUGS ARE NOW BEING APPROVED

5. **Kazia's Cantrixil drug has worked well in preclinical models of ovarian cancer**. The drug, which has multiple mechanisms of action, is the fruits of two decades of Kazia research around actives from soybean with anti-cancer properties. Cantrixil, for which Kazia has secured an Orphan Drug Designation from the FDA, will read out Phase 1 data in 2018.
6. **Kazia has upside in its former lead programme via Noxopharm**. Kazia's lead compound, when it was called Novogen, was an isoflavone analogue with anti-cancer activity called Phenoxodiol. Another company called Noxopharm (ASX: NOX) is now developing a new formulation of Phenoxodiol called NOX66, and, under a December 2017 collaboration agreement, Kazia is supporting the NOX66 programmes through the supply of certain technical and related proprietary information. In return for this support Kazia received a 4.9% equity stake in Noxopharm. That company expects to be in Phase 2/3 clinical studies by next year.
7. **Kazia has a quality leadership team with a good business approach**. Kazia's CEO, Dr James Garner, brings valuable drug development experience gained at the Top 50 Pharma companies Takeda and

[4] Where the code is KZIA. The ratio of ADRs to ordinary shares is 10 to 1.
[5] Generic name copanlisib, see www.aliqopa.com.

Sanofi. Backing Garner is an experienced board Chaired by the turnaround specialist Iain Ross which includes the former Lilly executive Bryce Carmine.

8. **Kazia has the potential to rapidly create shareholder value.** Under Kazia's new leadership team, which was largely installed in 2016, the company will now seek to in-license undervalued assets from other pharma companies, develop those assets, and then out-license or sell them at a premium. We see this strategy has having potential to yield significant shareholder value in a relatively short time horizon of two-to-four years.
9. **Kazia has the cash to get started in the clinic with GDC-0084**. As at December 2017 Kazia had A$6.6m in cash and after the collection of near-term receivables, including an R&D tax rebate, there is around A$15m in current assets. Kazia is therefore funded to start the upcoming Phase 2 study.
10. **Kazia is undervalued on our numbers**. We value Kazia at $0.73 per share base case and $3.50 cents per share optimistic case. Our target price of $2.10 per share sits at the midpoint of our valuation range. We see Kazia being re-rated in part by the progress into the clinic of GDC-0084.

GDC-0084 – A potential new glioblastoma drug

GDC-0084, Kazia's lead compound, was originally developed by Genentech. The global rights to this anti-cancer small molecule, originally developed by Genentech and subsequently out-licensed by that company after a Phase 1 study, were obtained by Kazia in October 2016[6]. Kazia commenced a Phase 2 for GDC-0084 in March 2018. The provenance of GDC-0084 is encouraging. Genentech, the San Francisco-based company that pioneered the biotechnology industry in the 1970s and 1980s, is widely regarded as one of the most successful biotech companies ever, with a track record of developing highly innovative blockbuster drugs beginning with Humulin and subsequently including Rituxan, Herceptin and Avastin. Genentech was fully acquired by Roche[7] in 2009 in a transaction that valued the American company at >US$100bn[8], but Roche has since allowed Genentech to keep functioning as an independent operation to preserve the unique corporate culture.

GENENTECH HAS BEEN ONE OF THE WORLD'S MOST SUCCESSFUL BIOTECH COMPANIES

We expect good things from GDC-0084, for two reasons. Firstly, as an inhibitor of the cellular signalling pathway called PI3K, it follows along behind the first approved PI3K inhibitor, Zydelig[9], a Gilead drug which gained FDA approval in July 2014[10]. Secondly, with its pharmacology permitting the drug to pass above the blood-brain-barrier, there is potential for Kazia's PI3K inhibitor to be used in the treatment of brain cancers such as Glioblastoma Multiforme, which is where GDC-0084's Phase 2 will be conducted, and which is an important area of unmet clinical need. To understand why GDC-0084 has strong potential in glioblastoma as well as other cancers,

[6] The molecule was licensed directly from Genentech to Kazia, which paid the US company US$5m upfront. At the time of the transaction Kazia also paid A$0.6m cash and A$1.5m in shares to acquire the privately held Glioblast Pty Ltd. That company had previously been formed by two Sydney-based bio-entrepreneurs, Paul Hopper and Leslie Chong, with GDC-0084 in mind. Hopper and Chong are currently Chairman and CEO respectively of the peptide vaccine developer Imugene (ASX: IMU, www.imugene.com). Leslie Chong had had operational responsibility for GDC-0084 when at Genentech's gRED unit (Genentech Research and Early Development). Kazia will issue the Glioblast vendors A$1.25m in shares on commencement of GDC-0084's Phase 2 and another A$1.25m in shares on completion of that study.
[7] Roche (Basel, Switzerland, VTX:ROG, www.roche.com) is now the world's 3rd largest pharma company with US$39.6bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[8] Roche paid US$46.8bn cash for the 44% that it didn't already own.
[9] Generic name idelalisib - see www.zydelig.com.
[10] For three rare blood cancers - relapsed Chronic Lymphocytic Leukemia (CLL), follicular B-cell Non-Hodgkin Lymphoma and Small Lymphocytic Lymphoma (SLL).

let's look first at the idea of signalling pathways as cancer targets, then look at GDC-0084's particular pathway, PI3K, before looking at what we know about GDC-0084's effectiveness in a pre-clinical and clinical setting.

Signal transduction inhibition – a core cancer treatment paradigm. Inside the cell, a 'pathway' is a set of proteins that, activated sequentially, instruct the cell to perform some function, such as grow or divide. The signal starts when an initial protein or other molecule attaches to the external part of a receptor within the cell membrane. The resulting signal is then passed to the internal part of the receptor and from there through a cascade of enzymes called kinases as well as various transcription factors and other molecules, until the relevant cellular function is performed, and the signal goes away. Should the signalling pathway become faulty through mutations in key molecules within the pathway, the result is often a cancer cell. Signalling pathways take their name from key molecules within the pathway, such as NFkB, MAPK, JAK/STAT and the target of Kazia's drug, PI3K. Such pathways have long been of interest to cancer researchers because the multitude of mutated proteins in any particular cancer tend to group around a relatively small number of pathways[11], providing clues for the development of targeted drugs that can impact multiple faulty proteins at once, and thereby increase the chance of killing the cancer cell. This approach first mainstreamed in cancer therapy around 2001 with FDA approval of Gleevec, the first of the so-called signal transduction inhibitors. That drug, by its action on the BCR-ABL pathway, provided strong outcomes for patients with Chronic Myelogenous Leukemia (CML)[12]. Other highly successful signal transduction inhibitors have included Genentech's Tarceva (working through the EGFR signalling pathway) for lung cancer, BMS's Sprycel for CML (the BCR-ABL and SRC signalling pathways) and Pfizer's Sutent for kidney cancer (the VEGF and c-Kit signalling pathways).

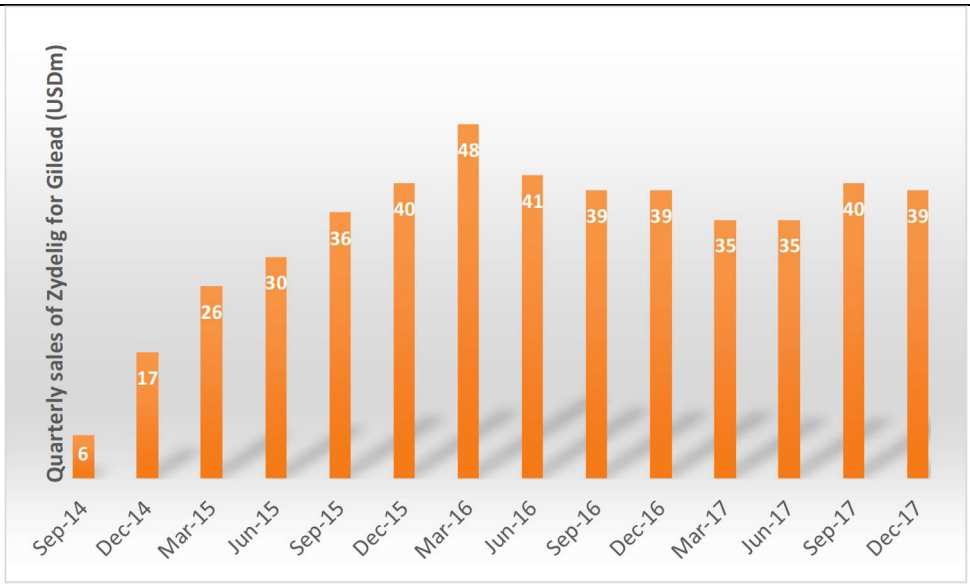
SIGNAL TRANSDUCTION PATHWAYS HAVE BECOME IMPORTANT CANCER TARGETS

PI3K – A particularly attractive signalling pathway. PI3K, short for Phosphoinositide 3-Kinase, has over the years proved a particularly interesting pathway for cancer drug developers. In the decade after PI3K was first identified in 1984[13] researchers were to find that this kinase, when linked with two downstream kinases - Akt, discovered in 1991[14], and mTOR, discovered in 1994[15] - formed perhaps the most commonly activated signalling pathway in cancer[16]. Mutations in the pathway can not only make the cell cancerous, since PI3K controls things like cell cycle progression[17], metabolism[18] and motility[19], but such mutations can also promote cancer through PI3K's involvement in factors such as angiogenesis[20] and inflammatory cell recruitment[21]. The main attraction of PI3K for drug developers today is threefold. Firstly, after more than three decades of research, the pathway is now well understood[22]. Secondly, it's a factor in many cancers. Thirdly, and perhaps most importantly, the pathway is quite

[11] For example, the laboratory of Bert Vogelstein, a cancer geneticist at Johns Hopkins, analysing the genetics of pancreatic cancer, found an average of 63 genetic alterations per cancer type but that these pathways defined a core set of only 12 signalling pathways (see Science. 2008 Sep 26;321(5897):1801-6. Epub 2008 Sep 4).
[12] A Kazia Scientific Advisory Board member, Dr Alex Matter, was formerly Global Head of Oncology Research for Novartis, where he played an instrumental role in bringing Gleevec to market. Alex Matter is now with Singapore's A*Star.
[13] By the noted American cell biologist Lewis Cantley, among others– see Nature. 1985 May 16-22;315(6016):239-42. Cantley is now at Weill Cornell Medicine.
[14] Proc Natl Acad Sci U S A. 1991 May 15;88(10):4171-5.
[15] Nature. 1994 Jun 30;369(6483):756-8.
[16] Nat Rev Drug Discov. 2009 Aug;8(8):627-44.
[17] Cell Cycle. 2003 Jul-Aug;2(4):339-45.
[18] Mol Biol Rep. 2015 Apr;42(4):841-51.
[19] J Natl Cancer Inst. 2013 Mar 20;105(6):393-404. Epub 2013 Jan 25.
[20] Front Mol Neurosci. 2011 Dec 2;4:51.
[21] Clin Cancer Res. 2013 May 1;19(9):2342-54. Epub 2013 Mar 13.
[22] Basically, PI3K phosphorylates a molecule called PIP2, which generates PIP3. That molecule in turn induces an array of kinases including Akt to move to the cell membrane to be activated. Akt regulates many proteins involved in cell growth, proliferation, motility, adhesion, neovascularisation, and apoptosis. Akt's activity then feeds into mTOR, which serves as master regulator of cell growth responding to numerous environmental inputs including the availability of oxygen, ATP and so on. For an overview see Pharmacol Ther. 2014 May;142(2):164-75. Epub 2013 Dec 9.

druggable, meaning that the various kinases involved have multiple sites where drugs can be made to bind[23]. It has also been suggested that cancer's 'addiction' to PI3K would allow cells to die more easily once that kinase was knocked out[24]. In addition, many other well-known cancer targets, such as EGFR and HER2, signal at least partly through the PI3K pathway, and so there is an opportunity for PI3K inhibitors to enhance the effects of drugs targeting these other mechanisms.

Figure 1: Zydelig has been a US$160m drug for Gilead



PI3K now has its first approved drugs. From the 1990s on, large and small companies proceeded to develop drugs aimed at one of more parts of the PI3K/Akt/mTOR pathway as well as variant versions thereof[25]. An early approach was to go after mTOR, since that protein is the 'mammalian Target of Rapamycin', rapamycin being a known, and later approved, immunosuppressant drug[26]. The result was two anti-cancer mTOR inhibitors that were rapamycin analogues[27] – Pfizer's Toricel[28], FDA approved in 2007, and Novartis' Afinitor[29], FDA approved in 2009[30]. Others have worked on Akt where there are no approved drugs at present[31]. However, it was PI3K that represented the holy grail of research in this area, because of its upstream position in the pathway and because shutting down mTOR seemed to over-activate PI3K[32]. For PI3K inhibition there were three basic approaches – the pan-class I PI3K inhibitors[33] that would work across all relevant PI3K types; isoform-selective PI3K inhibitors that worked against one or more or the four types – α, β, γ and δ – and dual pan-class I PI3K/mTOR inhibitors. The results from these

GILEAD'S ZYDELIG HAS VALIDATED PI3K AS A DRUG TARGET

[23] Curr Mol Pharmacol. 2010 Jun;3(2):79-90.
[24] Curr Oncol Rep. 2010 Mar;12(2):87-94.
[25] Nat Rev Drug Discov. 2014 Feb;13(2):140-56.
[26] See Semin Oncol. 2009 Dec;36 Suppl 3:S3-S17. Rapamycin, discovered in the early 1970s, finally gained FDA approval in 1999 for Wyeth as a prophylaxis for kidney transplant rejection.
[27] Rapamycin itself is not suitable as an anti-cancer agent due to its immunosuppressive effects.
[28] Generic name temsirolimus, see.www.toricel.com.
[29] Generic name everolimus, see www.afinitor.com.
[30] Another approach has been to try active-site mTOR inhibitors – see, for example, Biochem Pharmacol. 2012 May 1;83(9):1183-94. Epub 2012 Jan 26.
[31] One ASX-listed company focused on Akt is Prescient Therapeutics (Melbourne, Australia, ASX: PTX, www.prescienttherapeutics.com), whose PTX-200 compound, an Akt inhibitor, is currently in clinical studies in breast and ovarian cancer as well as Acute Myeloid Leukaemia.
[32] Mol Cancer Ther. 2014 Nov;13(11):2477-88. Epub 2014 Oct 16.
[33] There are three classes of PI3K but only Class I, which can function as a second-messenger in intracellular signalling, has been implicated in the development of cancer.

various programmes were mixed until Gilead, now the world's 7th largest pharma company[34], generated strong Phase 3 data in Chronic Lymphocytic Leukemia for Zydelig, an isoform-selective PI3K inhibitor that targeted the δ isoform[35]. That drug, as we noted above, gained FDA approval in 2014[36], justifying the US$375m upfront price tag (plus US$200m in milestones) for its original developer, the Seattle-based Calistoga Pharmaceuticals, which Gilead acquired in 2011 when Zydelig was in Phase 2. Zydelig is now a >US$100 p.a. drug. More recently, Bayer[37], the world's 16th largest pharma company, gained FDA approval in September 2017 for Aliqopa for the treatment of relapsed follicular lymphoma, on the basis of Phase 2 data[38]. Aliqopa is a pan-PI3K inhibitor. The Gilead/Calistoga and Bayer successes have helped maintain interest in PI3K inhibition as a treatment paradigm, suggesting as they do a path forward for this new drug class[39]. We expect significant momentum for PI3K inhibitors should the US cancer drug developer Verastem[40] gain FDA approval for Duvelisib, a dual inhibitor of PI3Kδ and PI3Kγ that performed well in Phase 3 in relapsed or refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma[41] and for which Verastem has now filed for FDA approval.

GDC-0084 is a PI3K inhibitor with a difference. GDC-0084 arose out of a long-standing research effort at Genentech to create new PI3K inhibitors. Specifically, the Genentech team was looking for orally available Class I PI3K inhibitors that could cross the blood-brain barrier, since there are activating mutations the PI3K pathway in over 80% of cases of the brain cancer known as glioblastoma[42]. An early effort saw the discovery of a number of inhibitors of the PI3Kα isoform that had this capability but didn't have a long enough half-life[43]. By around 2011 or 2012 the Genentech scientists had come up with GDC-0084[44], a pan-PI3K/mTOR inhibitor that had the requisite stability and was blood-brain penetrating. Genentech published this work in 2016[45].

GDC-0084 has encouraging early-stage data in high grade glioma. In 2012 Genentech took GDC-0084 into a Phase 1 study in patients with glioma where the disease was progressive or recurrent and high-grade[46]. Glioma is a cancer of the glial cells that provide the 'structural backbone' of the brain through their support of the neurons. There are four grades of glioma depending on disease severity, and for this study Genentech recruited 47 grade 3 and 4 patients (ie more severely affected) for an open label dose escalation study. This study found that GDC-0084 crossed the blood-brain barrier, had an acceptable tolerability profile, and seemed to be effective in many patients, with 40% (19 patients) showing stable disease. Interestingly, 26% (12 patients) of the PET scans showed a 'metabolic partial response', meaning that the brain, by taking up less of a glucose analogue called

THE PHASE 1 DATA FOR GDC-0084 LOOKS PROMISING

[34] Gilead Sciences (Foster City, Ca., Nasdaq:GILD, www.gilead.com) had US$30bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[35] N Engl J Med. 2014 Mar 13;370(11):997-1007. Epub 2014 Jan 22.
[36] The Phase 3 results became available in late 2013 – see the Gilead press release dated 18 November 2013 and headlined *'Gilead's Idelalisib significantly reduces rate of disease progression or death in Phase 3 Chronic Lymphocytic Leukemia study'*.
[37] Bayer (Berlin, Germany, ETR:BAYN, www.bayer.com) had US$16.9bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[38] See the Bayer press release dated 17 May 2017 and headlined *'Bayer receives FDA Priority Review for investigational anti-cancer compound Copanlisib'*.
[39] Nat Rev Clin Oncol. 2013 Mar;10(3):143-53. Epub 2013 Feb 12.
[40] Cambridge, Ma., Nasdaq: VSTM, www.verastem.com.
[41] Essentially the same disease – cancer of the lymphocytes – but in different locations, with CLL in the bloodstream and the bone marrow and SLL in the lymph nodes.
[42] Nature. 2008 Oct 23;455(7216):1061-8. Epub 2008 Sep 4.
[43] J Med Chem. 2012 Sep 27;55(18):8007-20. Epub 2012 Sep 11.
[44] See WO/2012/082997, priority date 16 December 2010.
[45] ACS Med Chem Lett. 2016 Feb 16;7(4):351-6.
[46] See NCT01547546 at www.clinicaltrials.gov.

fludeoxyglucose, probably had less glucose-hungry tumour cells in it[47]. Genentech reported this data at ASCO 2016, the annual meeting that year of the American Society of Clinical Oncology[48].

Why Kazia has taken GDC-0084 into Phase 2 with glioblastoma. The highest grade of glioma is glioblastoma, which is a cancer of a kind of glial cell called the astrocyte. Glioblastoma is often called Glioblastoma Multiforme or GBM because the individual lesions tend to have different shapes. Glioblastoma has been in the news in the US in the last two years due to the 2015 death from the disease of Beau Biden, son of then Vice President Joe Biden[49], and the July 2017 diagnosis of a leading Republican Senator, John McCain of Arizona. As much of the media coverage has noted[50], the thing about glioblastoma is the low life expectancy of the patient – historically five-year survival was only 2-4%[51], and while temozolomide has improved the survival picture somewhat since FDA approval in that setting in 2005, the improvement in medial Overall Survival has probably only been a couple of months – from 12 months to 14[52]. Moreover, temozolomide only seems to work if the tumour has 'MGMT promoter methylation'[53], which happens in perhaps 40-50% of the patient population[54]. Consequently, there is opportunity for any agent – and that agent is likely to be a small molecule given the 'immunologically privileged' nature of the brain[55] – which can show a survival advantage over temozolomide. Glioblastoma may be the most common of the brain cancers[56], but it only affects approximately 10,000 people per year in the US[57], so that it's an Orphan Drug opportunity. GDC-0084 was granted Orphan Drug Designation by the FDA in February 2018. We believe, in spite of the small population size, that glioblastoma can be a 'company maker' for Kazia given a potential global market of at least half a billion US dollars, and potentially more than a billion dollars[58]. We outline our thinking on market size below.

GLIOBLASTOMA IS A SIGNIFICANT MARKET OPPORTUNITY FOR KAZIA

GDC-0084's Phase 2 commenced in March 2018. An important part of the GDC-0084 story for Kazia is what the Australian company inherited from Genentech with the programme, namely, an open IND and enough manufactured drug (ie 45 kg) to support a Phase 2. The Phase 1 also had some quality trial sites – UCLA in Los Angeles, Dana-Farber and MassGen in Boston, MD Anderson in Houston and Vall d'Hebron in Barcelona. All this has enabled the Kazia team to move quickly, to the point where Kazia was able to initiate its Phase 2 in March 2018. Kazia has designed a 228-patient randomised two-arm study managed by the CRO Chiltern Oncology[59] in

[47] Cells when they turn cancerous have higher levels of glucose metabolism. One of the things that awoke research interest in glucose metabolism in cancer was the PI3K/Akt/mTOR pathway, which has an evolutionarily conserved function in metabolism – see Nat Rev Cancer. 2016 Oct;16(10):635-49. Epub 2016 Sep 16.
[48] The poster for the study, headlined '*A first-in-human Phase 1 study to evaluate the brain-penetrant PI3K/mTOR inhibitor GDC-0084 in patients with progressive or recurrent high-grade glioma*', is available on Kazia's web site.
[49] This was one of the factors which motivated Vice President Biden to lead the much-vaunted 'cancer moonshot' initiative – see *What Is the point of Joe Biden's Cancer 'Moonshot'?* by David Graham, The Atlantic, 11 February 2016.
[50] See, for example, *Glioblastoma, John McCain's form of brain cancer, carries troubling prognosis* by Denise Grady, New York Times, 20 July 2017.
[51] See J Neurooncol. 1998 Nov;40(2):151-60 and Can J Public Health. 2016 Jun 27;107(1):e37-42.
[52] J Neurooncol. 2012 Apr;107(2):359-64. Epub 2011 Nov 2.
[53] MGMT, a gene located at chromosome 10q26, codes for a DNA repair enzyme. If the gene is methylated, it is silenced, meaning less DNA repair, making the glioblastoma cells susceptible to the effect of temozolomide - see J Cell Physiol. 2018 Jan;233(1):378-386. Epub 2017 May 16.
[54] Fam Cancer. 2013 Sep;12(3):449-58.
[55] Interestingly, Celldex Therapeutics (Needham, Ma., Nasdaq: CLDX, www.celldextherapeutics.com) generated some good Phase 2 data with Rintega (rindopepimut), a peptide vaccine which targeted the EGFRvIII antigen in glioblastoma, but this approach didn't work in Phase 3 (see Lancet Oncol. 2017 Oct;18(10):1373-1385. Epub 2017 Aug 23). Companies are still trying out immunology-based approaches. MN-166 (ibudilast), a cytokine inhibitor with apparent anti-neuroinflammatory properties from MediciNova (La Jolla, Ca., Nasdaq: MNOV, www.medicinova.com), is being prepared for a Phase 2 study in recurrent Grade IV glioblastoma at Royal North Shore Hospital in Sydney - see the MediciNova press release dated 5 June 2017 and headlined *'MediciNova announces positive results from a glioblastoma animal model study presented at the 2017 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois'*.
[56] Glioma is roughly 80% of all brain cancer and glioblastoma is 50% of the gliomas – see Neuro Oncol. 2012 Nov;14 Suppl 5:v1-49.
[57] Estimated using the American Cancer Society's annual Cancer Facts and Figures estimates.
[58] See Novogen's April 2017 corporate presentation, slide 10.
[59] A CRO is a Clinical Research Organisation to whom drug companies outsource the conduct of clinical trials. Chiltern is now a part of LabCorp's Covance CRO business – LabCorp bought it in July 2017 for US$1.2bn.

which patients are recruited over ~60 sites after the usual standard of care – ie debulking surgery followed by temozolomide and radiation. Patients will randomise 1:1 to either maintenance temozolomide or GDC-0084. Kazia's investigators will commence their study with a lead-in component to optimise dosing – since the Phase 1 study was conducted in heavily pre-treated patients, the maximum tolerated dose in a first-line setting for GDC-0084 with maintenance temozolomide may in fact be higher than the 45 mg once daily found in the Phase 1. The company expects recruitment to take about 18 months, helped by the speed with which many patients can become temozolomide-resistant. Follow-up will be over 12 months, so first preliminary data is expected to read out 12-15 months after commencement of recruitment. We expect that some or all of the Phase 1 sites will be part of the Phase 2 given the earlier encouraging outcomes[60].

Why Genentech out-licensed GDC-0084 to Kazia. We believe that Genentech was willing to outsource the GDC-0084 programme not because of any fault in the drug so much as there were already PI3K candidates in the clinic for both Genentech and Roche. Outlicensing of compounds by Big Pharma has become more common in recent years[61], as evidenced most recently by Eli Lilly's July 2017 decision to seek external partners for seven programmes, six of which were at Phase 1 and 2[62]. The divestitures are often driven by strategic change in the company – witness Pfizer's outlicensing in 2011 of a Phase 2 tyrosine kinase inhibitor candidate called neratinib to a newly formed company called Puma Biotechnology[63], in part because it had come from Wyeth (which Pfizer had acquired in 2009) and didn't fit Pfizer's post-Wyeth strategy. That compound is now Nerlynx, FDA approved in July 2017 for HER2+ breast cancer, and Puma is a US$2.4bn company[64]. Two other notable Nasdaq-listed emerging companies that got their start in-licensing compounds from Big Pharma are Tesaro and Axovant Sciences[65]. For the Kazia /Genentech transaction, consider that Genentech's parent, Roche, is currently working on Taselisib[66], an inhibitor of the α, γ, and δ isoforms, in HR-positive metastatic breast cancer, squamous non-small cell lung cancer, and other solid tumours, while Genentech is in Phase 1 with a PI3Kα inhibitor called GDC-0077. A third PI3K inhibitor in such cases can look surplus to requirements. And in any case, Roche can acquire Kazia in the event of clinical success – it paid US$175m in 2008 to acquire the London-based PI3K drug developer Piramed Pharma. The existing Roche/Genentech PI3K programmes are moving forward on the basis that biomarkers will be developed that are expected to help predict treatment success[67]. Biomarker development hasn't been done for GDC-0084 ahead of the Phase 2, and Kazia believes that it will be difficult to find good biomarkers relevant to glioblastoma that would circulate in the bloodstream. The low survival threshold for glioblastoma suggests that the Australian company can still succeed without biomarkers, however should it be necessary to evaluate patients' blood samples in a *post hoc* analysis looking for biomarkers, we believe that such biomarkers could be identified given the research success of other groups in recent years[68].

THE GENENTECH / KAZIA DEAL HAS PRECEDENTS

[60] Kazia has flagged that it has '*experienced clinical sites enthusiastic to participate*' in the Phase 2 – see the company's September 2017 corporate presentation, slide 2.
[61] See *Why is pharma out-licensing its compounds?* by John LaMattina, Forbes, 29 October 2012.
[62] See *Lilly puts two-thirds of midphase cancer pipeline up for sale in major shake-up of R&D priorities* by Nick Paul Taylor, FierceBiotech, 25 July 2017.
[63] Los Angeles, Ca., NYSE: PBYI, www.pumabiotechnology.com.
[64] 2 April 2018 close on Nasdaq.
[65] For background on Tesaro see Appendix VII of this note. Axovant Sciences (New York, NY, Nasdaq: AXON, www.axovant.com) is a CNS drug developer founded in 2015 to pick up GSK's RVT-101, an Alzheimer's candidate that had completed several Phase 2 studies. RVT-101, now called Intepirdine, is a 5-HT6 receptor antagonist. The drug failed at Phase 3 in mild-to-moderate Alzheimer's in September 2017 and in Lewy Body Dementia in January 2018. Axovant is now focused on nelotanserin, is a selective inverse agonist of the 5HT2A receptor which may be useful in sleep disorders related to Parkinson's and Lewy Body Dementia.
[66] Formerly GDC-0032.
[67] See *Following the right path(way)* by Lori Friedman, Genentech, 4 April 2014.
[68] Metabolism. 2015 Mar;64(3 Suppl 1):S22-7. Epub 2014 Oct 30.

Table 1: Big Pharma out-licensings to small companies

Out-licensor	In-licensee	Date
Merck & Co.	Miikana Therapeutics	May-05
Biogen	Stromedix	May-07
Novartis	Santhera	Jul-07
Roche	Ore Pharmaceuticals	Jul-08
Amgen	Atara Biotherapeutics	Oct-12
GSK	Padlock Therapeutics	May-15

The GDC-0084 Phase 2 may allow early approval. In 2009 the FDA granted Genentech's monoclonal antibody drug Avastin[69] accelerated approval as a single agent for glioblastoma patients with progressive disease following prior therapy. The Agency did so mainly on the basis of a Phase 2 study called AVF3708g in 167 patients[70] which showed an Objective Response Rate of 28%[71]. We believe, given the relative lack of a survival advantage for existing treatments, that GDC-0084 has potential to qualify for similar accelerated approval after the Phase 2, so long as it turns in a good number on the primary endpoint, which is Progression-Free Survival (PFS). Avastin's PFS in recurrent glioblastoma is around 3.5 months[72].

GDC-0084 COULD GET ACCELERATED APPROVAL

Why some observers of the cancer drug development space might be sceptical of GDC-0084's prospects moving into Phase 2. Given the lack of success of most PI3K inhibitors since the first one entered the clinic around 2006, Kazia's acquisition of its candidate may look risky. One is reminded of the title of a 2013 paper in the Swiss journal *Frontiers in Oncology* entitled '*Targeting PI3K in Cancer: Any Good News?*'[73]. It's fair to say that the first batch of pan-PI3K inhibitors didn't yield exciting results. For example, the Novartis drug dactolisib, a dual PI3K/mTOR inhibitor, demonstrated limited efficacy and tolerability in a Phase 1b study with Afinitor in advanced solid tumours[74]. Similarly, when Genentech added its pan-PI3k inhibitor pictilisib to AstraZeneca's Faslodex in ER+ breast cancer at Phase 2, it didn't significantly improve PFS because pictilisib dosing ran into various toxicities[75]. It has been suggested that, since PI3Kα and PI3Kβ are expressed ubiquitously and serve essential cellular functions, pan-PI3K inhibitors may ultimate struggle on the tolerability front, and that isoform selectivity as per Zydelig is the way to go[76]. Two emerging drug developers with PI3K inhibitor candidates appear to have taken this view – IPI-549 from Infinity Pharmaceuticals[77] is an inhibitor of the γ isoform in Phase 1 while Umbralisib from TG

[69] Generic name bevacizumab, www.avastin.com. Avastin, which targets VEGF, had gained its first FDA approval in 2004, for metastatic colorectal cancer.
[70] See NCT00345163 at www.clinicaltrials.gov.
[71] Drugs. 2010;70(2):181-9.
[72] This reflects data from Genentech's CABARET study, which showed that adding carboplatin to bevacizumab in this setting would be effective – see Neuro Oncol. 2015 Nov;17(11):1504-13. Epub 2015 Jun 30.
[73] Front Oncol. 2013 May 8;3:108.
[74] Target Oncol. 2017 Jun;12(3):323-332.
[75] Lancet Oncol. 2016 Jun;17(6):811-821. Epub 2016 May 4.
[76] The reason Zydelig worked, this line of reasoning suggests, is that the PI3Kδ isoform is almost exclusively expressed in the hematopoietic lineage, making it suitable as a target for blood cancers like CLL – see Clin Cancer Res. 2015 Apr 1;21(7):1537-42. Epub 2015 Feb 10.
[77] Cambridge, Ma., Nasdaq: INFI, www.infi.com. Interestingly, Infinity was the original developer of the abovementioned Duvelisib drug, the PI3Kδ/PI3Kγ inhibitor with which Verastam has now succeeded at Phase 3 in Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma. Infinity backed away from this drug in 2016 after a Phase 2 study in refractory indolent Non-Hodgkin Lymphoma met its primary endpoint of Overall Response Rate (46%) but only with partial responses. Infinity sold the drug to Verastem in November 2016 for US$28m in milestones.

Therapeutics[78] is a δ inhibitor in Phase 3[79]. Maybe Genentech had such concerns in mind when it gave GDC-0084 to Kazia Therapeutics. However, we would argue that the recent Phase 2 success[80] and approval of Aliqopa changes the picture on pan-PI3K inhibitors. That drug is a pan-PI3K inhibitor but is predominantly active against the α and δ isoforms. Before Aliqopa the record of Novartis' Buparlisib, a pan-PI3K inhibitor, had given cause for cautious optimism as far as the pan-PI3K approach goes. The Buparlisib Phase 3 study called BELLE-2, in HR-positive advanced breast cancer, shows Buparlisib plus Faslodex clearly outperforming in this setting, with median PFS of 6·8 months vs 4.0 months when the activation status of PI3K pathway is ascertained from biomarkers (p=0·014)[81]. Which shows that better drug design, combined with the use of biomarkers to predict treatment success, can lead to better PI3K drugs[82]. We say 'cautious optimism' because Buparlisib's toxicity in BELLE-2, noted most frequently in the form of elevated liver enzymes, has caused Novartis to think that an isoform-selective PI3K would be better for HR-positive breast cancer.

Why Kazia thinks it can succeed with GDC-0084. Kazia believes that GDC-0084's prospects are good because the drug was specifically designed with glioma and glioblastoma in mind. It may be a pan-PI3K/mTOR inhibitor but, by being designed to work above the blood-brain barrier, its propensity for off-target effects is reduced. It's also worth noting that Phase 1 didn't flag any toxicity issues other than those other PI3K/mTOR inhibitors have already shown - fatigue, hyperglycaemia, nausea, rash, diarrhea etc. The abovementioned Buparlisib, initially developed for breast cancer, has a history of mood disturbance as one of its adverse events, so that mood disorders are now part of the exclusion criteria in clinical trials[83] and the drug is therefore unlikely to be evaluated in brain cancer. The mood disturbances have been shown to be related to an off-target effect of tubulin binding[84], and are therefore unlikely to be a class effect with other PI3K inhibitors.

GDC-0084 WAS DEVELOPED WITH GLIOBLASTOMA IN MIND

PI3K remains attractive to Big Pharma. Various PI3K inhibitors are being developed by large Pharma companies, following on from Gilead's success with Zydelig. We noted above Roche's Taselisib and GDC-0077 compounds, as well as Novartis' Phase 3 work with Buparlisib. Novartis also has Alpelisib, a selective PI3Kα inhibitor, and Afuresertib, an Akt inhibitor, in the works. Other large pharma companies are also active - Pfizer is in Phase 1 with a dual PI3K/mTOR inhibitor called Gedatolisib (PF-05212384) while GSK is in Phase 1 with GSK2636771, PI3Kβ inhibitor[85]. We therefore expect that in the event of Phase 2 success Kazia will attract considerable licensing interest.

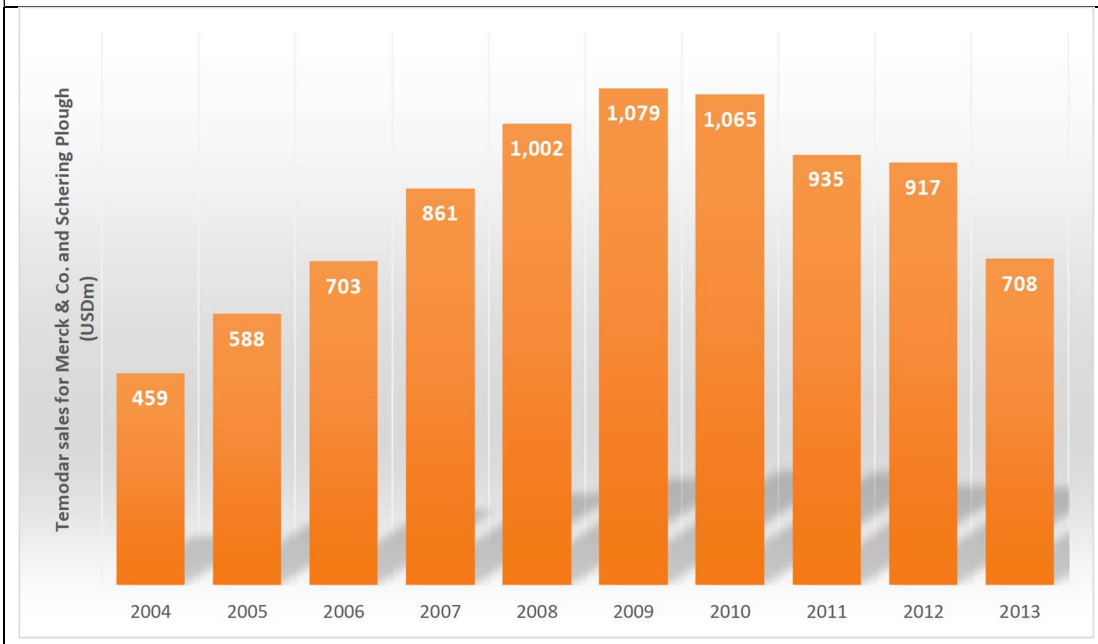
Glioblastoma is a half-billion-dollar market opportunity, at least. Obviously a PI3K inhibitor will have use across multiple cancers but we also think that glioblastoma alone is at least a US$500m opportunity, based on roughly 10,000 patients p.a. in the US and around 16,000 in Europe and modest pricing of only US$20,000 p.a., which would likely be cost effective even at a short increase in Overall Survival. The aforementioned temozolomide, an alkylating agent[86] marketed as Temodar, gained its first FDA approval for Schering-Plough in 1999. Its first

TEMODAR WAS A BLOCKBUSTER FOR SCHERING-PLOUGH

[78] New York, NY, Nasdaq: TGTX, www.tgtherapeutics.com.
[79] In combination with a TG-developed anti-CD20 monoclonal antibody called TG-1101. The indications here are CLL and NHL.
[80] Which was an open-label study in which a 103-patient subset of relapsed follicular lymphoma in a Non-Hodgkin Lymphoma study showed a 59% Objective Response Rate.
[81] Lancet Oncol. 2017 Jul;18(7):904-916. Epub 2017 May 30.
[82] For background from some Novartis researchers see Ann N Y Acad Sci. 2013 Mar;1280:19-23.
[83] See J Thorac Oncol. 2015 Sep;10(9):1319-1327 for a study in non-small cell lung cancer where grade 3 mood disorders still showed up in the Adverse Event count.
[84] Expert Opin Investig Drugs. 2015 Mar;24(3):421-31. Epub 2015 Feb 3.
[85] Clin Cancer Res. 2017 Oct 1;23(19):5981-5992. Epub 2017 Jun 23.
[86] Alkylating agents bind to DNA and prevent proper DNA replication.

indication, for refractory anaplastic astrocytoma, made it a US$400m drug but its second, and only other indication, in newly diagnosed glioblastoma, which granted in both the EU and the US in 2005[87], was worth another US$600m in extra sales as its potential developed in this indication over the next five years. Sales would likely have been much higher in glioblastoma had the drug worked regardless of MGMT methylation status. As for price, cost effectiveness in healthcare is the cost of switching treatments from the current standard of care to the new therapy, as given in costs per Quality-Adjusted Life Year (QALY)[88]. Traditionally in the US an ICER under US$50,000 per QALY was considered 'cost effective'[89] however in more recent years the threshold seems to have lifted to US$100,000 to account for healthcare inflation[90].

Figure 2: Temodar was a blockbuster drug for Merck & Co.



Cantrixil is set to read out first data in 2018

Cantrixil is an in-house discovery of Kazia's. Cantrixil, currently in a Phase 1 study in platinum-resistant ovarian cancer, is the fruits of Kazia's long-standing interest in benzopyrans as anti-cancer drugs. As we explain in Appendix Ia, Kazia Therapeutics as Novogen spent most of the period from 1996 to 2016 working on isoflavone analogues with anti-cancer activity, its most notable candidate being Phenoxodiol, which failed in a Phase 3 study in platinum-resistant ovarian cancer in June 2010. Phenoxodiol was created out of the benzopyran pharmacophore found in a soybean derivative called genistein. After Phenoxodiol's failure Novogen returned to

[87] It gained FDA approval in this indication in March 2005 – see Clin Cancer Res. 2005 Oct 1;11(19 Pt 1):6767-71.
[88] A 'quality adjusted' life year is one year of perfect health understood to be gained by the therapy. Two years of '50% health' are one QALY, as are three years of '30% health'. There is, the reader will appreciate, a certain subjectivity to such assessments.
[89] See Grosse SD, *Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold*, Expert Rev Pharmacoecon Outcomes Res. 2008 Apr;8(2):165-78.
[90] See BMJ. 2006 Mar 25;332(7543):699-703. Epub 2006 Feb 22.

work on benzopyrans with the aim of creating 'super-benzopyrans' with higher levels of activity. The result, by 2015, was Cantrixil, in whose early development Novogen drew upon a long-time collaboration with Professor Gil Mor's laboratory at Yale University. Cantrixil is simply a super-benzopyran drug called Trx-E-002-1, delivered using a commercially-available cyclodextrin carrier. The drug is intended to be delivered via direct injection into the peritoneal cavity, allowing higher exposure to metastasising ovarian cancer than would be the case with systemic delivery. Significantly, there is now solid pre-clinical evidence of Cantrixil's activity against ovarian cancer stem cells.

Cantrixil makes Kazia a cancer stem cell play. One of the more important steps forward for cancer research in the last two decades has been the discovery of the cancer stem cells, which are the hardy cells that can rebuild a tumour after conventional chemotherapy has killed most of the cancer in a patient's body. Since the first one was identified in 1994[91] cancer stem cells have been identified in most cancer types. The Mor laboratory at Yale became, in 2009, the first in the world to molecularly characterise ovarian cancer stem cells[92], showing that they expressed two cell surface markers, CD44[93] and MyD88[94]. The Mor lab has since demonstrated, *in vitro* and *in vivo*, that Cantrixil has activity against chemoresistant CD44+/ MyD88 ovarian cancer, in combination with cisplatin[95].

Cantrixil is now in Phase 1 in platinum-resistant ovarian cancer. The data on ovarian cancer stem cells made this indication the obvious first choice for Caxtrixil. The drug received Orphan Drug Designation from the FDA for ovarian cancer in April 2015 and Novogen took It into its Phase 1 in December 2016[96]. This 60-patient dose-ranging study is expected to take around 18 months to complete and read out data in 2018.

Ovarian cancer remains an area of unmet medical need in that there have been few developments since Bristol-Myers Squibb gained FDA approval for Taxol in December 1992[97]. The current five-year survival rate post diagnosis for the disease is relatively poor, at only 45%, with two-thirds of all cancer being detected once the disease has started to metastasise, where five-year survival is only 35%[98]. One recent item of progress is Genentech's success with Avastin – that drug, in combination with standard-of-care, showed a survival advantage in the GOG-0218 study as early as 2011. Genentech has recently filed for FDA approval of Avastin in this new indication. Even if Avastin joins the standard of care, we expect there will be continued demand for new therapies, since the GOG-0218 data on PFS has only shown a six-month improvement, from 12 months to 18, over carboplatin and Taxol[99].

TREATMENT OUTCOMES HAVE HISTORICALLY NOT BEEN GREAT FOR OVARIAN CANCER

Ovarian cancer is a billion-dollar market opportunity. There will be around 22,000 new cases of ovarian cancer in the US in 2017 while 14,000 women will die of the disease[100]. We argue that the global market for new ovarian cancer treatments is probably >US$1.5bn at modest pricing[101].

[91] The Canadian scientist Dr John Dick first identified them in leukaemia. See Nature. 1994 Feb 17;367(6464):645-8.
[92] Cell Cycle. 2009 Jan 1;8(1):158-66.
[93] Genet Mol Res. 2016 Aug 12;15(3).
[94] PLoS One. 2014 Jun 30;9(6):e100816.
[95] Mol Cancer Ther. 2016 Jun;15(6):1279-90. Epub 2016 Apr 8. See also Abstract 1519: '*Cantrixil targets ovarian cancer stem cells and prevents recurrence in a cisplatin-resistant animal model*' presented at AACR 2015.
[96] See NCT02903771 at www.clinicaltrials.gov.
[97] One recent development has been AstraZeneca's Lynparza (generic name olaparib, see www.lynparza.com), the first of the PARP inhibitors, which gained FDA approval in December 2014. Lynparza was initially indicated for BRCA-mutated advanced ovarian cancer, in effect as a fourth-line treatment. The drug was approved off the back of Phase 2 data showing a 34% Objective Response Rate (see Clin Cancer Res. 2015 Oct 1;21(19):4257-61. Epub 2015 Jul 17).
[98] Source: American Cancer Society: Survival Rates for Ovarian Cancer, by Stage.
[99] See the Genentech press release dated 25 October 2017 and headlined '*FDA accepts Genentech's supplemental Biologics License Application for Avastin as a front-line treatment for women with advanced ovarian cancer*'.
[100] Source: American Cancer Society, Cancer Facts and Figures 2017.
[101] See Novogen's April 2017 corporate presentation, slide 15.

Kazia has a few other interesting assets

A next-generation super-benzopyrans. As we note in Appendix Ia, when Kazia was primarily focused on super-benzopyrans it developed a whole library of them. One such super-benzopyran still at pre-clinical is Trilexium (TRXE-009). Kazia believes that this drug also acts, like Cantrixil, against cancer stem cells, and that it could potentially be used in an Orphan paediatric cancer such as neuroblastoma. In November 2017 Kazia announced that Trllexium had been spun out into a new company called Heaton-Brown Life Sciences[102], in return for a 10% equity in that company. Kazia will receive milestones and royalties related to its development.

Anti-tropomyosin drugs. Tropomyosin is a protein in the 'skeleton' of cells that helps the cell retain its shape. Tubulin, another cytoskeletal protein, is a well-characterised cancer target, with Taxol known to exert its anti-cancer effect through this mechanism. Tropomyosin, however, has yet to be properly targeted in cancer therapy. For a number of years Kazia funded a programme looking for an anti-tropomyosin drug which involved drugs specific for Tpm3.1, a particular tropomyosin common in cancer cells. An initial lead, called ATM-3507 or Anisina, generated interesting *in vivo* and *in vitro* data[103] but this programme was terminated in April 2017[104]. Anti-tropomyosin research looking for next generation inhibitors continues with grant funding.

A small but potentially valuable stake in 'Phenoxodiol 2.0[105].A Sydney-based company called Noxopharm, which went public on the ASX in mid-2016, is now pursuing a new formulation of Phenoxodiol, delivered rectally for the treatment of various cancers, most notably metastatic castrate-resistant prostate cancer. Under a December 2017 collaboration agreement, Kazia is supporting the development of Noxopharm's candidate, called NOX66, through the supply of certain technical and related proprietary information. In return Kazia received 5.3 million Noxopharm shares and 3 million 2020 options, with a market value of A$6.5m. At the time the Noxopharm shares represented 4.9% of the company. We profile Noxopharm in Appendix Ib of this note.

Valuing Kazia

We value Kazia at $0.73 per share base case and $3.50 per share optimistic case. Our target price of $2.10 per share represents a midpoint of these two valuations. Our approach was as follows:

- Our WACC was 15.2% (Speculative)[106].
- We modelled payoffs only for GDC-0084 and Cantrixil.

[102] Andrew Heaton and David Brown, co-founders of Heaton-Brown, were formerly Novogen scientists.
[103] Mol Cancer Ther. 2017 Aug;16(8):1555-1565. Epub 2017 May 18.
[104] For the relevant intellectual property over Anisina see WO/2015074124, WO/2015074123, WO/2016/008010 and WO/2016/187667.
[105] Sydney, Australia, ASX: NOX, www.noxopharm.com.
[106] For a relevant discount rate, we use WACCs of between ~11% and ~15% depending on the risk for Life Science companies. This is derived from a RFR of 2.6%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies); and an ungeared beta of 1.1. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

- We valued each programme on a probability-weighted DCF approach.
- We modelled around 15 years of commercial exclusivity for each product.

GDC-0084 – We assume Kazia takes this to market by itself. We assume that Kazia self-funds the upcoming Phase 2 for GDC-0084 (see below) and that the product is then granted accelerated approval after the study. Our valuation parameters for this scenario were as follows:

- Trial costs A$25m (optimistic case) to A$35m (base case)[107];
- Completion of Phase 2 in 2.5-4.5 years from early 2018, ie calendar 2020 to 2022, with accelerated approval between FY22 (optimistic case) and FY24 (base case);
- A 35% probability of clinical success, reflecting the historic success rates of small molecules in Phase 2 (38%), adjusting for the probability of FDA clearance for drugs that have completed the main clinical stages (91%)[108]
- Peak sales of US$700bn-$1.1bn, as per the kind of sales enjoyed by temozolomide across two indications;
- Total milestone payments both clinical and sales-related back to Genentech of US$20-40m, as well as a 3-6% royalty;
- Gross margins of 60-80%, improving 0.1%-0.2% p.a.;
- Distribution costs of 15-25% of revenue, improving 0.1-0.2% p.a.;
- A 10% market share post-exclusivity, with a 3-5% negative terminal growth rate;
- A 30% tax rate.

GDC-0084 MAY HAVE ACCELERATED APPROVAL BY FY22

Cantrixil - We assume Kazia Therapeutics partners this asset after the current Phase 1. We also assume

- US$5-10m more expenditure by Kazia Therapeutics on the project;
- A 13% probability of the drug gaining approval, as per the historic success rates for small molecules in Phase 1[109];
- A licensing in FY20 or FY21, for US$25-50m upfront, US$100-200m in milestones and a 7-11% royalty rate, consistent with historic deals such as the Merck/Endocyte deal of 2012[110];
- Product approval in FY26-FY27;
- Peak sales of US$400-600m;
- A 10% market share post-exclusivity for Kazia's licensee, with a 3-5% negative terminal growth rate;
- A 30% tax rate.

[107] That reflects costs of US$80,000-US$120,000 per patient, consistent with publicly available data – see, for example, Sertkaya et. al., *Examination of clinical trial costs and barriers for drug development*, submission to the Office of the Assistant Secretary of Planning and Evaluation, US Department of Health and Human Services, 25 July 2014.
[108] DiMasi et. al., Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.
[109] DiMasi et. al., op. cit.
[110] Endocyte's lead compound at the time was vintafolide, a folate-conjugated vinca alkaloid. The drug was granted Orphan Drug status in Europe in March 2012 and in April 2012 it was partnered to Merck & Co. in a deal worth up to US$1bn in upfront and milestones payable to Endocyte, including a US$120m upfront payment.

Table 2: NDF Research's valuation of Kazia Therapeutics

	Base	Optim.
GDC-0084 (A$m)	47.3	318.9
Cantrixil (A$m)	18.8	59.9
Total programme value	66.2	378.9
Value of tax losses	2.5	2.5
Corporate overhead	-33.1	-33.1
Cash now (A$m)	6.6	6.6
Cash to be raised (A$m)	40.0	40.0
Option exercises (A$m)	0.5	0.5
Total value (A$m)	82.7	395.4
Total diluted shares (million)	113.0	113.0
Value per share	$0.732	$3.500
Valuation midpoint	$2.116	
Share price now (A$ per share)	$0.750	
Upside to midpoint	182.1%	

Further capital. As at December 2017 Kazia had A$6.6m in cash and after the collection of near-term receivables, including an R&D tax rebate, there is around A$15m in current assets. On our estimates this would be insufficient to complete the GDC-0084 Phase 2. As a conservative base case scenario, we have therefore modelled a A$40m raising at 65 cents per share. We emphasise very strongly that this is an assumption for modelling purposes and does not mean Kazia will perform such a transaction, or that it will do so at this price. If the company were successful in raising money at a higher share price, then this would likely represent upside to the overall valuation. We believe that Kazia can raise the requisite capital if it chooses to, given the provenance of its lead molecule and the continued attractiveness to Life Science investors of PI3K inhibitors as a drug class.

Re-rating Kazia

We see a number of events helping to re-rate Kazia over the next 12 months:

- Publication by Genentech and its clinical investigators of the GDC-0084 Phase I data;
- Initiation of the GDC-0084 Phase 2;
- Data from the Cantrixil Phase 1;
- Initial data from the GDC-0084 Phase 2

WE SEE THE START OF THE GLIOBLASTOMA PHASE 2 AS HELPING TO RE-RATE KAZIA

Kazia's capable leadership team

Kazia has leadership with drug development experience. It is also a relatively new team. Dr James Garner joined in February 2016.

- CEO **Dr James Garner** previously worked in senior positions with the clinical trials organisation Quintiles[111] as well as the Top 50 pharma companies Takeda[112] and Sanofi[113], where he was involved in product development.

The Kazia board, which includes Garner, has all the elements one would look for in an emerging drug developer.

- Chairman **Iain Ross** brings a background working with established UK Life Science companies including Sandoz, Fisons, Roche and Celltech, as well as valuable experience turning around early-stage companies on behalf of banks and private equity groups. One of his Australian directorships is Anatara Lifesciences[114], a developer of oral solutions for gastrointestinal diseases.
- **Bryce Carmine** brings Big Pharma background, having spent decades as an executive in Eli Lilly, where, for instance, he engineered a major reorganisation of Lilly Bio-Medicines between 2009 and 2011.
- **Steven Coffey**, a partner of the Sydney accounting firm Watkins Coffey Martin, brings corporate skills.

Appendix Ia – The story so far

Kazia Therapeutics has been a drug development company publicly traded on ASX since September 1994. The company started life as Norvet Ltd, a veterinary pharmaceutical company. It became Novogen Ltd, keeping the original ASX Code of NRT, in 1997 kept that name for the next twenty years. It changed its name to Kazia Therapeutics in late 2017 to reflect the new company that stands today – purely focused on the commercialisation of a portfolio of world-class oncology assets, with an all-new team. For most of the time between 1997 and 2016 Novogen worked on synthetic flavonoid derivatives with anti-cancer properties. Cantrixil, a Kazia drug candidate currently in Phase 1 in platinum-resistant ovarian cancer, is one of the fruits of this long-standing research effort.

Novogen starts working on the anti-cancer properties of genistein derivatives, 1996-2000. Novogen's first iteration as a cancer drug developer, under the leadership of Dr Graham Kelly, involved a discovery programme centred on a component of soybean called genistein. Kelly had theories around the health benefits of various dietary isoflavones, and these theories had led Novogen to work on products such as Promensil, a red clover extract marketed OTC as a post-menopausal women's health supplement[115]. The genistein project was suggested by the long-standing belief that that isoflavones present in soy-rich foods was the reason why populations whose diet was high in soy products enjoyed much lower cancer incidence[116]. That theory made sense given that genistein is a tyrosine kinase inhibitor[117]. Novogen began around 1996 to work on the discovery of genistein derivatives and one of the products that its researchers synthesised was NV-06, later called Phenoxodiol[118]. By the

NOVOGEN PIONEERED WORK ON GENISTEIN DERIVATIVES

[111] Research Triangle Park, NC, NYSE: Q, www.quintiles.com.
[112] Takeda (Osaka, Japan, TSE: 4502, www.takeda.com) is the world's 19th largest pharma company with US$12.8bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[113] Sanofi (Paris, France, EPA:SAN, www.sanofi.com) is the world's 5th largest pharma company with US$34.2bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[114] Brisbane, Australia, ASX: ANR, www.anataralifesciences.com.
[115] www.promensil.com.au
[116] Cancer Invest. 2003;21(5):744-57. For a paper on the isoflavone hypothesis as it pertains to prostate cancer, which mentions Phenoxodiol, see Mol Biotechnol. 2005 Jul;30(3):253-70.
[117] Adv Exp Med Biol. 2004;546:121-65.
[118] See WO1998/08503, priority date 30 August 1996.

late 1990s this new signal transduction inhibitor, around 10 times more potent than the original genistein molecule, was Novogen's lead compound.

Novogen's Phenoxodiol makes it to Phase 3, 2000-2010. Novogen took Phenoxodiol into the clinic in early 2000[119], and within six years it was in late stage clinical development, funded by a Nasdaq-listed company that Novogen had formed in 2001 called Marshall Edwards. Post-discovery, various researchers established that Phenoxodiol had direct cytotoxic activity against multiple tumour types[120] and that part of this activity was as a topoisomerase II inhibitor[121]. The drug was also found to act as an anti-cancer immunomodulator at low concentrations[122], to have anti-angiogenesis properties[123], and even to have cancer chemopreventive effects[124]. The decision to focus Phenoxodiol on platinum-resistant ovarian cancer resulted from a close collaboration with Professor Gil Mor at Yale University which showed that the drug could sensitise chemoresistant ovarian cancer cells to platinum as well the taxanes[125] through Fas-mediated apoptosis[126]. After establishing in Phase 2 that Phenoxodiol worked well with cisplatin to overcome platinum-resistant in ovarian cancer[127], the drug was taken into a Phase 3 study called OVATURE in late 2006[128]. The difference between Phase 2 and Phase 3, however, was that Phase 2 saw Phenoxodiol delivered intravenously to sensitise cisplatin whereas Phase 3 switched to oral delivery to sensitise carboplatin, the latter drug being less toxic than cisplatin[129]. Ominously, the inclusion criteria for the Phase 3 specified a 'platinum-free interval of no greater than 6 months at the time of enrolment'. This may be why recruitment into this study was slow, since platinum-free intervals of less than six months are generally considered unable to restore platinum sensitivity[130]. In April 2009 Marshall Edwards closed recruitment at only 141 out of a planned 340 patients enrolled[131], and, after analysis of this cohort, the US company reported in June 2010 that there had been no statistically significant improvement in either PFS or OS[132].

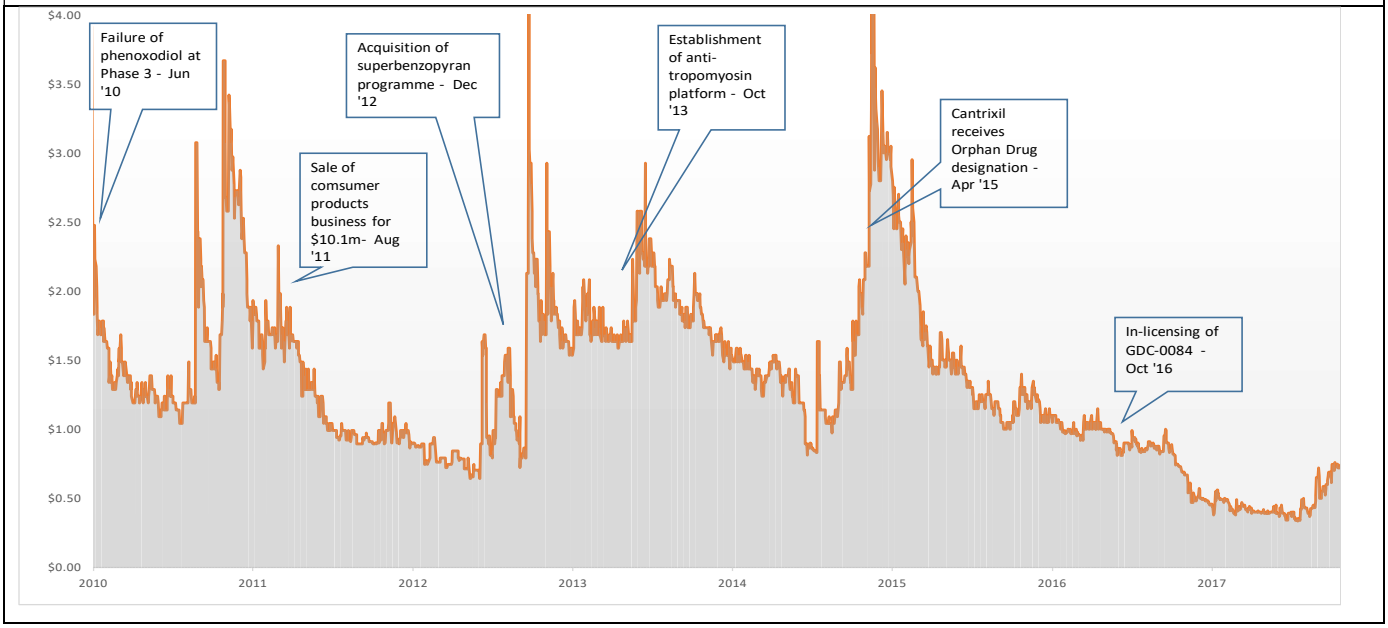
NOVOGEN TOOK A DRUG TO PHASE 3

Novogen rebuilds around super-benzopyrans, 2010-2016. After the Phase 3 failure of Phenoxodiol, Novogen divested itself of most of its programmes into Marshall Edwards, now called MEI Pharma[133], and then sold its shares in that company. From late 2012 Novogen rebuilt around a new drug concept called the super-benzopyrans. Phenoxodiol is a benzopyran molecule, meaning that its chemical structure involves fusions of benzene rings (C_6H_6) and pyran rings (C_5H_6O). Novogen and Marshall Edwards had over the years experimented with the benzopyran concept to create other anti-cancer drugs with more potency such triphendiol[134], NV-128[135] and ME-344[136]. Graham Kelly, who had left Novogen in 2007, had formed a new private company called Triaxial

[119] See the Novogen market release dated 7 February 2000 and headlined '*Anti-cancer drug enters Phase 1 clinical trials*'.
[120] Including prostate cancer – see J Biosci. 2012 Mar;37(1):73-84 and Cancer Cell Int. 2014 Nov 8;14(1):110.
[121] Anticancer Res. 2002 Sep-Oct;22(5):2581-5.
[122] J Cell Mol Med. 2009 Sep;13(9B):3929-38. Epub 2009 Feb 11.
[123] Int J Cancer. 2006 May 15;118(10):2412-20.
[124] Eur J Cancer. 2003 May;39(7):1012-8.
[125] See Curr Opin Investig Drugs. 2006 Jun;7(6):542-8 and Expert Opin Pharmacother. 2009 Apr;10(6):1059-67.
[126] Oncogene. 2003 May 1;22(17):2611-20. Apoptosis is 'programmed' cell death, that is, death that is naturally-occurring. Cancer cells tend to avoid apoptosis. Fas, discovered in 1989, is a cell-surface protein which, when it binds to another protein called FasL, triggers a pathway which results in apoptosis.
[127] Int J Gynecol Cancer. 2011 May;21(4):633-9.
[128] OVATURE stood for OVArian TUmor Response - see NCT00382811 at www.clinicaltrials.gov.
[129] Semin Oncol. 1995 Oct;22(5 Suppl 12):88-90.
[130] Cancer. 2017 Sep 15;123(18):3450-3459. Epub 2017 Jul 5.
[131] See the Novogen market release dated 14 April 2009 and headlined '*Marshall Edwards Inc. to undertake analysis of Ovature data*'.
[132] See the market release by the Novogen affiliate Marshall Edwards dated 1 June 2010 and headlined '*Marshall Edwards announces final results from halted Phase 3 clinical trial of Phenoxodiol*'. The data was published in 2013 in the journal *Annals of Oncology* – see Ann Oncol. 2014 Jan;25(1):160-5. Epub 2013 Dec 5.
[133] San Diego, Ca, Nasdaq: MEIP, www.meipharma.com.
[134] Anticancer Drugs. 2011 Sep;22(8):719-31.
[135] Cancer. 2009 Jul 15;115(14):3204-16.
[136] Cancer. 2015 Apr 1;121(7):1056-63. Epub 2014 Nov 19.

Pharmaceuticals to work on even more complex benzopyrans, which he called super-benzopyrans. Triaxial had created a platform which it called VAL-ID[137] which allowed various chemical moieties to be attached to the benzopyran core, and used it develop a library of new super-benzopyran drugs specific for cancer stem cells. Kazia Therapeutics acquired Triaxial in December 2012 and Graham Kelly returned as CEO. The first candidate from the Triaxial platform was CS-6, which showed activity against ovarian cancer stem cells[138]. From late 2013 Novogen collaborated on this drug with Yale's Gil Mor. The two groups formed a company called CanTX, 85%-owned by Kazia Therapeutics and proceeded to develop new therapies. Kazia Therapeutics licensed Cantrixil (TRX-E-002-1) into this entity for development as an ovarian cancer treatment. The product made it into a Phase 1 study in December 2016 which is expected to read out data in the first half of 2018. Trilexium (TRXE-009), a 'second generation' super-benzopyran (ie second generation compared to CS-6), emerged from the VAL-ID platform around 2013 and is currently in the lead optimisation stage in a new company called Heaton-Brown Life Sciences. 2013 also saw Novogen begin work on anti-tropomyosin drugs, in collaboration with a privately-held company called Genscreen[139]. Kazia remains interested in this programme although it terminated preclinical development around a product called ATM-3507 in April 2017.

Figure 3: Novogen/Kazia's roller coaster ride since 2010



Novogen transitions to GDC-0084 under James Garner, from 2015. Kazia Therapeutics went through a significant transition from 2015. James Garner joined as the new CEO and Graham Kelly left to work with Noxopharm[140], which is now pursuing a new way to deliver Phenoxodiol rectally. Garner's approach for Kazia Therapeutics, as we noted above, has been to in-license clinical stage assets, develop them, and then out-license

[137] Versatile Approach to Library-based Iterative Design.
[138] See Novogen's market release of 18 February 2013.
[139] See Novogen's market release dated 9 October 2013 and headlined '*Novogen acquires new technology to add to its oncology drug pipeline*'.
[140] Sydney, Australia, ASX: NOX, www.noxopharm.com.

them. That led to the acquisition of GDC-0084 in October 2016 and the name change to Kazia Therapeutics in November 2017.

Appendix Ib – Kazia's stake in 'Phenoxodiol 2.0'

Kazia has a small but potentially valuable stake in 'Phenoxodiol 2.0'. We noted above that a Sydney-based company called Noxopharm is now pursuing a new formulation of Phenoxodiol. Under a December 2017 collaboration agreement, Kazia is supporting the development of Noxopharm's candidate, called NOX66, through the supply of certain technical and related proprietary information. In return Kazia received stock in Noxopharm representing 4.9% of the company. Noxopharm stock was 98 cents per share at the time. After a capital raising announced in March 2018 at 90 cents per share, valuing Noxopharm at A$107m. Kazia's may contractually be entitled to receive additional stock in order to retain its proportional level of ownership.

Noxopharm believes it has developed a Phenoxodiol formulation that can work. Noxopharm was founded by Graham Kelly in 2015 in order to develop insights that he had had regarding the reasons for Phenoxodiol's Phase 3 clinical failure in platinum-resistant ovarian cancer in 2010, which we profile in Appendix 1a. Kelly believed that the effectiveness of Phenoxodiol had been foiled by 'Phase 2 metabolism', where the attachment of an ionised group to the drug renders it more water soluble and therefore easier to excrete in urine. Many drugs that are processed by Phase 2 metabolism are still able to exert a therapeutic effect while in their active form pre-metabolism[141]. Kelly theorised that Phase 2 metabolism of Phenoxodiol through the attachment of glucuronic acid or sulphate had reduced the amount of the active form to therapeutically negligible levels[142]. Kelly's solution to the Phase 2 metabolism problem was to formulate Phenoxodiol, which he now referred to as 'idronoxil', in a proprietary lipid called 'Liprose'[143] that would prevent the attachment of glucuronic acid or sulphate. To further avoid any Phase 2 metabolism, the drug would be delivered as a rectal suppository. Kelly called the new idronoxil formulation NOX66 and filed for patent protection[144].

The NOX66.001 study suggests that NOX66 plus chemotherapy can bring about disease stabilisation in late-stage patients. This maiden clinical study of NOX66, now being conducted in Georgia[145], was initiated in April 2017 and combines NOX66 with carboplatin in a variety of solid tumours. Noxopharm announced interim data from this study in November 2017, reporting that, after three months of NOX66 plus low-dose carboplatin, 10 of 11 evaluated patients had no disease progression on the RECIST criteria, and that the drug combination had been safe and well-tolerated. Further data in March 2014 showed stable disease in 12 or 14 patients after three months.

NOX66 plus radiotherapy may bring about an abscopal effect in some patients. Noxopharm is currently conducting or preparing for several radiotherapy studies in which NOX66 is administered alongside palliative

[141] Aspirin being a classic example – see Clin Pharmacokinet. 1985 Mar-Apr;10(2):164-77.
[142] This makes sense in the light of an earlier finding that Phenoxodiol has a very short half-life even when given intravenously - see BMC Clin Pharmacol. 2011 Feb 3;11:1.
[143] Short for 'Lipid Protective Shield'.
[144] See *Isoflavonoid composition with improved pharmacokinetics*, WO/2017/173498; *Targeted drug delivery*, WO/2017/173497; *Radiotherapy improvements*, WO/2017/173496; *Improvements in cancer treatment*, WO/2017/173474; and *Chemotherapy improvements*, WO/2017/181242. All have an April 2016 priority date.
[145] ie the former Soviet Republic, capital Tibilisi. Historically clinical trials conducted in Eastern Europe have had issues (see, for example, *A clinical trial torpedoed by fraud and incompetence* by Derek Lowe, Science Translational Medicine blog, 17 April 2017), but some have argued that these have tended to decline in recent years (see *Clinical trials Eldorado based on quality, not cost* by Anthony King, Euro Scientist, 26 November 2014).

radiotherapy to selected lesions. A remarkable early observation in the use of NOX66 with radiotherapy – first noted *in vivo*[146] – is an abscopal effect in which treatment of some tumours leads to the disappearance of tumours at a distance from the treatment lesions. Noxopharm presented two abscopal response case studies from a Compassionate Use programme at the Annual Scientific Meeting of the Trans-Tasman Radiation Oncology Group in March 2018.

What Noxopharm can potentially do for Kazia. Obviously Kazia's equity stake in Noxopharm is non-core, however we see potential for this stake to gain in value over time. Should the abscopal effect of NOX66 plus radiotherapy bear itself out in future clinical work it's reasonable to expect the market to respond favourably. In addition to this Noxopharm as it moves into Phase 2/3 studies can come to be regarded as more of a 'late-stage' opportunity.

Appendix II – A Kazia glossary

Accelerated approval – Early approval of a drug based on the use of a surrogate endpoint.

Active – Short for Active Pharmaceutical Ingredient (API), the part of a drug with pharmaceutical activity as opposed to a mere 'support' role.

Anisina (ATM-3507) – An anti-tropomyosin molecule targeting the Tpm3.1 protein, a critical structural component of cancer cells. Development of this programme by Novogen/Kazia Therapeutics was cancelled in 2017.

Apoptosis – 'Programmed' cell death, that is, death that is naturally-occurring. Cancer cells tend to avoid apoptosis.

ATM – Short for anti-tropomyosin.

Benzopyran – A chemical structure involving fusions of benzene rings (C_6H_6) and pyran rings (C_5H_6O).

Biomarker – A natural substance used as an indicator of a biological state, especially to detect the presence or severity of disease.

Blood-brain barrier – A wall of cells which line the blood vessels in the brain so tightly that only selected substances are permitted to pass through.

Cancer stem cell – A cell that can give rise to a tumour. Cancer stem cells traditionally have been difficult to kill with conventional chemotherapy and radiotherapy.

Cantrixil (TRXE-002-1) – A super-benzopyran developed by Kazia Therapeutics for the treatment of ovarian cancer. The active in this product is encapsulated in a cyclodextrin.

Cyclodextrin – Sugar molecules made from starch and often used as solubilising excipients for drug delivery. Because cyclodextrins possess a hydrophobic core and hydrophilic exterior, they can be used water-soluble drug carriers for hydrophobic injectable drugs.

[146] See the Noxopharm market release dated 3 March 2017 and headlined '*Noxopharm researching rare abscopal response*'.

Cytoskeleton – The network of protein fibres, particularly microfilaments, that gives shape to a cell.

Debulking – A reduction in the volume of a tumour, generally achieved by surgical removal.

FDA – The Food and Drug Administration, the American government body which regulates the pharmaceutical industry and from whom approval must be received before a drug can be marketed in the US.

GDC-0084[147] – A PI3K inhibitor originally developed by Genentech for which Kazia Therapeutics acquired global rights in October 2016.

Genistein – An isoflavone which has a benzopyran at its core that resembles the female sex hormone estradiol.

Glioblastoma Multiforme (GBM) – A rare brain cancer that begins in the glial cells that surround and support neurons.

IND – Short for Investigational New Drug application, a request filed with the FDA for authorisation to conduct human trials of a new drug or biological product in the United States.

Intraperitoneal – Injections into the peritoneum, the serous membrane that forms the lining of the abdominal cavity.

In vitro – Latin for 'in glass', referring to data obtained through testing in a test tube.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Isoflavones – Plant-based compounds which give colour to food and are noted for their antioxidant, anti-inflammatory and anti-cancer health benefits.

Isoform – Any of several different forms of the same protein.

Microtubules – 'Train-track'-like structures within a cell, which route nutrients and molecules around the cell.

MTD – Maximum Tolerated Dose.

Objective Response Rate – The rate at which tumours shrink as a result of medical treatment, where the response is measured by the RECIST criteria. RECIST, short for the Response Evaluation Criteria in Solid Tumours, is a set of rules that define when a tumour has responded to treatment, is stable, or has progressed.

Overall Survival (OS) – The percentage of subjects in a clinical trial who have survived for a defined period of time.

Phase – A stage of the clinical trialling process for a drug candidate. Phase 1 tests for safety. Phase 2 tests for efficacy in a small sample. Phase 3 tests for efficacy in a large sample.

Phenoxodiol – An isoflavone derivative developed by Novogen in the 1990s.

PI3K – Short for phosphoinositide 3-kinase, a family of cellular enzymes that plays a critical role in the regulation of cell proliferation and survival.

[147] Chemical name 5-(6,6-Dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[4,3-e]purin-2-yl)pyrimidin-2-amine.

PI3K/Akt/mTOR – A signal transduction cascade within cells where PI3K, Akt and mTOR are key 'nodes' within the pathway. The PI3K pathway is central to many physiological functions, including cell cycle, cell survival, angiogenesis etc, which makes the pathway important in the development of cancer.

Progression-Free Survival (PFS) – The length of time a cancer patient undergoing treatment can see no worsening of his or her cancer.

Small molecules – Drugs that have a low molecular weight (<500 daltons), making them easier to penetrate cell membranes and the blood-brain barrier.

Solid tumour – In cancer, a tumour that is a localised mass of tissue rather than a blood cancer like leukaemia.

Super-benzopyran (SBP) – A class of small molecule developed by Novogen/Kazia since the mid-1990s and originally based on genistein.

Temozolomide – A cancer drug which gained FDA approved as Temodar in 1999 and which is commonly used to treat glioblastoma.

Tpm3.1 – A tropomyosin protein. Tpm3.1 is the target of Novogen/Kazia's former Anisina drug candidate.

Trilexium (TRXE-009)– A super-benzopyran molecule which was developed by Kazia Therapeutics and was assigned to a new company called Heaton-Brown Life Sciences in late 2017.

Tropomyosin – A structural protein of the actin cytoskeleton that has been implicated in actin filaments turning cancerous.

TRXE-002-1 – See Cantrixil.

TRXE-009 – See Trilexium.

Appendix III – Kazia's IP position

GDC-0084. This compound is covered by *Tricyclic Pi3k inhibitor compounds and methods of use*, WO/2012/082997, priority date 16 December 2010[148], invented by Jennafer Dotson, Robert Heald, Timothy Heffron, Graham Jones, Sussie Krintel, Neville Mclean, Chudi Ndubaku, Alan Olivero, Laurent Salphati, Lan Wang and Binqing Wei.

Cantrixil. This compound is covered by *Functionalised benzopyran compounds and use thereof*, WO/2015/117202[149], priority date 7 February 2014, invented by Andrew Heaton, David Brown and Graham Kelly.

[148] This patent was granted in the US as No. 8,883,799 (November 2014) and No. 9,546,182 (January 2017). In Europe it was granted as EP 2 651951 (November 2014) and EP 2 813506 (May 2016).
[149] This patent was granted in the US as No. 9,701,655 in July 2017. In the original PCT patent application, Yale's Ayesha Alvero and Gil Mor are listed as co-inventors but that is not the case on US Patent No. 9,701,655, on the basis that the contributions of Alvero and Mor were merely 'supportive' rather than instrumental.

Appendix IV – Kazia's capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code KZA (million)	48.4	83.2%	
Listed options (million)	3.1	5.4%	Average exercise price $4.00, average expiry date 04-Jun-2020
Unlisted options (million)	4.8	8.2%	Average exercise price $3.05, average expiry date 21-Nov-2020
Convertible notes	1.9	3.2%	$0.46m in notes convertible when any Novogen programme completes Phase 2 or receives Breakthrough Therapy Designation
Fully diluted shares	58.2		

Current market cap:	A$36.3 million (US$27.9 million)
Current share price	$0.750
Twelve month range	$0.34 - $0.80
Average turnover per day (last three months)	86,100

Note: The December 2017 Kazia/Noxopharm transaction saw the convertible note liability reduce from $0.6m to $0.46m.

Appendix V – Kazia's major shareholders

Kazia currently has only one substantial shareholder:

- **Hishenk Pty Ltd (11.2%)**, owned by Michael Abolakian, whose Hyecorp Property Group[150] is a Sydney-based property developer and investor.

Appendix VI – Papers relevant to Kazia

Alvero et. al. (2016), *TRX-E-002-1 induces c-Jun-dependent apoptosis in ovarian cancer stem cells and prevents recurrence* in vivo. Mol Cancer Ther. 2016 Jun;15(6):1279-90. Epub 2016 Apr 8 (full text available for free online).

- This paper presents data in the efficacy of Cantrixil against ovarian cancer *in vivo*.

[150] www.hyecorp.com.au.

Currier et. al. (2017), *Identification of cancer-targeted tropomyosin inhibitors and their synergy with microtubule drugs*, Mol Cancer Ther. 2017 May 18. [Epub ahead of print]

- This paper covers *in vitro* and *in vivo* work on ATM-3507 in neuroblastoma.

Desouza-Armstrong et. al. (2017), *Tumor suppressor tropomyosin Tpm2.1 regulates sensitivity to apoptosis beyond anoikis characterized by changes in the levels of intrinsic apoptosis proteins*. Cytoskeleton (Hoboken). 2017 Jun;74(6):233-248. Epub 2017 Apr 26.

- This paper covers the likely mechanism of action for an anti-tropomyosin drug.

Glass et. al. (2015), *Hypoxia alters the recruitment of tropomyosins into the actin stress fibres of neuroblastoma cells*. BMC Cancer. 2015 Oct 16;15:712 (full text available for free online).

- This paper explores a possible use for future anti-tropomyosin drugs, namely, that they would be synergistic with drugs that induce cellular hypoxia (that is, starve the cell of oxygen).

Heffron et. al. (2016), *Discovery of clinical development candidate GDC-0084, a brain penetrant Inhibitor of PI3K and mTOR*. ACS Med Chem Lett. 2016 Feb 16;7(4):351-6. eCollection 2016 Apr 14 (full text available for free online).

- This paper discusses how the Genentech scientists sought to develop a PI3K inhibitor that penetrated the blood-brain barrier and was metabolically stable.

Saif et. al. (2017), *Pharmacology and toxicology of the novel investigational agent Cantrixil (TRX-E-002-1).* Cancer Chemother Pharmacol. 2017 Feb;79(2):303-314. Epub 2016 Dec 24 (full text available for free online).

- This paper covers the animal toxicology work on Cantrixil.

Salphati et. al. (2016), *Brain distribution and efficacy of the brain penetrant PI3K Inhibitor GDC-0084 in orthotopic mouse models of human glioblastoma*. Drug Metab Dispos. 2016 Dec;44(12):1881-1889. Epub 2016 Sep 16.

- This paper covers the *in vivo* work showing that GDC-0084 could penetrate above the blood-brain barrier.

Appendix VII – Companies to watch

Companies involves in glioblastoma

- **Agenus.** This company, which in recent years has focused mainly on antibodies to immune checkpoints[151], was originally built an adjuvant technology called QS-21 Stimulon[152] and a personalised cancer vaccine technology called Prophage that uses heat shock proteins extracted from a patient's tumour. In October 2017 a GSK shingles vaccine adjuvanted with QS-21 gained FDA approval. Agenus is looking to take Prophage into Phase 3 in newly diagnosed glioblastoma after favourable Phase 2 work which showed that PD-L1 expression was an important biomarker for treatment success with the potential for possibly >40 months median Overall Survival[153].
- **DelMar Pharmaceuticals**. This company's lead compound is VAL-083, an alkylating agent that readily crosses the blood-brain barrier. Off the back of encouraging Phase 1/2 work[154], this drug is being taken into various studies including a Phase 3 in recurrent glioblastoma to evaluate Overall Survival versus salvage chemotherapy.
- **Diffusion Pharmaceuticals**. This company's lead product, a synthetic carotenoid called Trans Sodium Crocetinate (TSC), is designed to restore chemosensitivity to tumours by re-oxygenating the hypoxic micro-environment. At Phase 2 in glioblastoma TSC increased Overall Survival by 37% against historical controls[155]. Diffusion Pharmaceuticals took this product to Phase 3 in early 2018.
- **GW Pharmaceuticals**. This company brought to market Sativex, the world's first plant-derived cannabinoid prescription drug, for the treatment of spasticity due to Multiple Sclerosis. Epidiolex, an oral solution of pure plant-derived cannabidiol, is in Phase 3 for various conditions including the form of epilepsy known as Dravet Syndrome. Deeper in the GW pipeline is a cannabinoid product in Phase 2 for glioma. Cannabinoids are known to act on signalling pathways involved cancer cell proliferation and survival[156]. In a Phase 2 study in recurrent glioblastoma a GW proprietary combination of tetrahydrocannabinol and cannabidiol recorded 83% one-year survival versus 53% for placebo (p=0.042)[157].
- **Inovio.** This DNA vaccine developer, whose technological strength is the way in which the vaccine constructs are electroporated into cells, is in Phase 3 with a DNA vaccine which targets the E6 and E7 proteins of HPV to treat cervical dysplasia. Inovio's glioblastoma vaccine will be studied at Phase 1/2 with a PD-1 inhibitor from Regeneron[158] called REGN2810[159].

[151] Immune checkpoints are molecules in the immune system that either turn up a signal (co-stimulatory molecules) or turn down a signal.
[152] A saponin derived from soap bark tree native to Chile (*Quillaja saponaria*), long known to have immunostimulatory properties.
[153] PD-L1, the ligand to the immune checkpoint PD-1, is upregulated in glioblastoma – see Oncotarget. 2017 Jun 27;8(26):42214-42225.
[154] See the ASCo 2016 poster headlined '*Phase I/II study of dianhydrogalactitol in patients with recurrent glioblastoma*'.
[155] J Neurosurg. 2017 Feb;126(2):460-466. Epub 2016 May 13.
[156] Curr Oncol. 2016 Mar;23(2):S23-32. Epub 2016 Mar 16
[157] See the GW Pharma press release dated 7 February 2017 and headlined '*GW Pharmaceuticals achieves positive results in Phase 2 proof of concept study in glioma*'.
[158] Regeneron Pharmaceuticals (Tarrytown, NY, Nasdaq:REGN, www.regeneron.com) is the world's 39th largest pharma company with US$3.3bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[159] See the Inovio press release dated 8 May 2017 and headlined '*Inovio & Regeneron enter immuno-oncology clinical study agreement for glioblastoma combination therapy*'.

- **Midatech Pharma.** This company has been built around technology to conjugate drugs to gold nanoparticles for targeted release. The company has developed a pre-clinical glioblastoma candidate called MTR103 which is able to go above the blood-brain barrier.
- **Moleculin Biotech**. This company's lead compound is Annamycin, an anthracycline for the treatment of relapsed or refractory Acute Myeloid Leukemia. Annamycin, known to have less cardiotoxicity than doxorubicin[160], is a lipophilic form of that drug with the ability to bypass multidrug resistance mechanisms. Annamycin is expected to enter the clinic in 2018. WP1066, a STAT3 inhibitor, and WP1122, a glucose analogue designed to interfere with cancer metabolism, are both being prepared for glioblastoma indications.
- **Mustang Bio.** This cancer immunotherapy company, whose focus is the emerging treatment approach called CAR-T[161], is in Phase 1 with MB-101, a CAR which expresses a target on glioblastoma cells called IL13Rα2[162].
- **Northwest Biotherapeutics**. This cellular therapy's technology, called DCVax, allows dendritic cells to be programmed to generate an anti-cancer immune response. Specifically, the therapy involves sourcing monocytes from the patient, fully or partially maturing them into dendritic cells depending on whether or not the tumour is resectable, and then exposing those cells to all the full set cancer-related antigens taken from the patient's tumour. DCVax is currently in Phase 3 in glioblastoma, where Phase 1/2 work generated favourable survival data even in patients with early tumour re-growth[163].
- **Novocure**. This company is pioneering a cancer treatment approached called TTFields in which electric fields tuned to specific frequencies are used to disrupt cancer cell division. The company's Optune product gained FDA approval for the treatment of recurrent glioblastoma in 2011 and for newly diagnosed glioblastoma in 2015. In newly diagnosed glioblastoma the PFS and OS gain is about three months on top of standard of care[164]. Novocure is now working on approval for other indications.
- **Tocagen.** This gene therapy company uses retroviral replicating vectors to deliver a gene called cytosine deaminase into cancer cells. When the patient takes the antifungal agent 5-FC, the cytosine deaminase converts the 5-FC into the antimetabolite agent 5-FU. The first indication for this approach, called Toca 511 & Toca FC, is high-grade glioma. Toca 511 & Toca FC has been granted Breakthrough Therapy Designation for this indication by the FDA. In Phase 1 in recurrent high-grade glioma, Overall Survival at 13.6 months beat external controls[165]. A Phase 3 study reads out data in 2018.
- **Tracon Pharmaceuticals**. This drug developer's lead compound is TRC105, a monoclonal antibody which targets endoglin, a protein involved in angiogenesis. TRC105 is in Phase 3 in angiosarcoma and is in clinical development in a number of other cancers while the ophthalmic use of the drug has been

[160] The anthracyclines are antibiotics with anti-tumour properties. Doxorubicin, a notable cancer drug from the 1970s, is probably the most widely used of the anthracyclines.
[161] CAR-T is a form of adoptive T cell therapy, in which a patient's own T cells are engineered to increase their cancer-fighting properties. In CAR-T the T cells are engineering to carry chimeric antigen receptors (CARs), these receptors being a combination of antibodies and T cell signalling molecules.
[162] Clin Cancer Res. 2015 Sep 15;21(18):4062-72. Epub 2015 Jun 9.
[163] See the Northwest Bio press release dated 27 March 2015 and headlined *'NW Bio reports promising survival data in 51 GBM patients treated with DCVax-L'*.
[164] Curr Opin Neurol. 2015 Dec;28(6):659-64.
[165] Sci Transl Med. 2016 Jun 1;8(341):341ra75.

partnered with the Japanese pharma company Santen. TRC102 is a small molecule that prevents breaks in DNA from being repaired. It is in Phase 2 in glioblastoma and mesothelioma.

- **VBI Vaccines**. This company develops vaccines based on enveloped Virus-Like Particles (eVLPs). The company already has one marketed prophylactic vaccine, for Hepatitis B, and is using its eVLP platform to develop therapeutic vaccines for cytomegalovirus (CMV) infection and for glioblastoma. The glioblastoma candidate, now in Phase 1, targets two CMV antigens, on the theory that there is some association between the two diseases[166].

- **Vascular Biogenics**. This gene therapy company's lead candidate is ofranergene obadenovec (VB-111), now in a Phase 3 trial for recurrent glioblastoma under a Special Protocol Assessment from the FDA[167]. This product is a viral vector where the transgene is the Fas gene which causes cells to under apoptosis, and where the promoter for the transgene, called PPE-1-3X, only activates in the endothelial cells of angiogenic blood vessels. In Phase 2 this product, in combination with Avastin, showed 15 months median survival in progressive glioblastoma where there was 'continuous exposure' to the gene therapy, versus 8 months for 'limited exposure'[168].

- **Ziopharm Oncology**. This immuno-oncology company is a player in the CAR-T area through technology which allows the non-viral transfer of relevant genes[169]. A number of Ziopharm-developed CAR-T products are now in Phase 1. Ziopharm is also working on the clinical application in oncology of 'RheoSwitch', a gene expression system developed by Intrexon[170]. A RheoSwitch product for IL-12 called Ad-RTS-hIL-12 has generated median Overall Survival in recurrent or progressive glioblastoma of >12 months at Phase 1[171]. A pivotal trial is currently being prepared.

Companies involved in ovarian cancer

- **Adaptimmune Therapeutics**. This company, a pioneer of the immuno-oncology approach called 'adoptive T cell therapy', has been built on technology for engineering increased affinity T-cell receptors (TCRs), achieved via *in vitro* molecular evolution involving phage display. The company's lead product is an engineered TCR to the cancer antigen NY-ESO-1, for which it is in Phase 2/3 studies in synovial sarcoma and in multiple myeloma. A major partnering deal with GSK in June 2014 could see that company could pay US$350m over the period to 2021 for enhanced TCR-engineered autologous T cells targeting NY-ESO-1 and other targets. Adaptimmune is in a Phase 1/2 study with its NY-ESO-1 TCR therapeutic in treatment-resistant Stage 3/4 ovarian cancer.

[166] J Neurooncol. 2015 Jul;123(3):465-71. Epub 2015 Feb 15.
[167] A Special Protocol Assessment is a prior agreement with the FDA that if a clinical trial meets certain endpoints, the drug being trialled will be approved. This ensures that the FDA can't change its mind and ask for further data when the final results come in.
[168] See the VBL Therapeutics press release dated 28 September 2015 and headlined '*VBL Therapeutics reports full Phase 2 data from clinical trial of VB-111 in recurrent glioblastoma (rGBM) at the ECC 2015 conference, meeting the primary endpoint of statistically-significant increase in Overall Survival*'.
[169] The 'Sleeping Beauty' gene transfer system is based on a transposon, which allows gene transfer without the usual viral vector methods which some observers of the gene therapy space consider unsafe. See Adv Genet. 2005;54:189-232.
[170] San Carlos, Ca., Nasdaq: XON, www.dna.com. Intrexon is a pioneer in the field of synthetic biology. A major shareholder in both Intrexon and Ziopharma is the bio-entrepreneur Randal Kirk.
[171] See the Ziopharm press release dated 18 September 2017 and headlined '*ZIOPHARM Oncology announces updated findings from Phase 1 study of Ad-RTS-hIL-12 + Veledimex in recurrent glioblastoma presented at American Academy of Neurological Surgery Annual Meeting*'.

- **Array BioPharma**. This cancer drug developer is in five Phase 3 studies with various small molecules. Ipatasertib (GDC-0068), an Akt inhibitor partnered with Genentech, is in Phase 3 in prostate cancer. Motolimod, an agonist of the immune system activator TLR-8 designed to prompt an anti-cancer immune response, is in Phase 2 in ovarian cancer and head and neck cancer.

- **Celsion**. This company's original technology involved heat-sensitive liposomes that deliver conventional chemotherapy drugs to cancer cells, for activation by an external heating device. Celsion's original Phase 3 trial of ThermoDox, which is heat-activated doxorubicin, missed its primary endpoint of PFS in primary liver cancer, however a new Phase 3 treating a sub-group identified in the earlier study is now underway. Celsion's second technology, called 'TheraPlas', is a polymer-based gene delivery system. The first candidate from this technology is GEN-1, which delivers interleukin 12 for localised anti-cancer immunotherapy. That product is in Phase 1 in ovarian cancer.
- **ImmunoGen**. This company is a player in antibody-drug conjugates (ADCs) through its Targeted Antibody Payload technology, which was the basis of Roche's Kadclya (trastuzumab emtansine), where the antibody is Roche's earlier blockbuster Herceptin. Kadclya gained FDA approval in 2013. ImmunoGen's Mirvetuximab soravtansine ADC, for the treatment of folate receptor alpha positive cancer, is in Phase 3 in ovarian cancer.

- **Immunovaccine**. This company has been built on a liposome-in-oil vaccine adjuvanting delivery platform called 'DepoVax', where the antigen+adjuvant complex is encapsulated in a liposome and then suspended in oil. This water-free formulation allows the creation of a depot effect upon vaccination that presents the antigens and adjuvant to the immune system for a prolonged period of time. The company's DPX-Survivac vaccine, which combines Depovax with the cancer antigen survivin, is in Phase 2 in ovarian cancer in combination with the Merck & Co. PD-1 inhibitor Keytruda.

- **Iovance Biotherapeutics**. This adoptive T cell therapy company takes Tumor-Infiltrating Lymphocytes from patients, expands their number considerably, and then returns them to the patient after lymphodepletion with cytoxan and fludarabine. The lead indications are in metastatic melanoma in conjunction with various agents, however a Phase 2 is contemplated in ovarian cancer.

- **NuCana**. This company takes nucleoside analogue drugs and adds to them a 'phosphoramidate' motif to improve cellular penetration and overcome the key cancer resistance mechanisms of the original drug. The company's lead compound, Acelarin, is a phosphoramidate prodrug of a gemcitabine. Nucana is working towards Phase 3 studies of Acelarin in biliary cancer and pancreatic cancer. After a Phase 1b with carboplatin in recurrent ovarian cancer that saw a 96% disease control rate, the drug is now in Phase 2 in that setting.

- **OncoMed Pharmaceuticals**. This cancer drug developer's lead compounds are two monoclonal antibodies – Navicixizumab, a bispecific antibody that targets DLL4 in the Notch cancer stem cell pathway as well as VEGF receptors, and Rosmantuzumab, which targets a pathway called RSPO-LGR. Navicixizumab is in Phase 1b in ovarian and colorectal cancers.

- **Syndax Pharmaceuticals.** This company's lead product, an HDAC inhibitor[172] called Entinostat, is in Phase 3 for advanced HR+ breast cancer, where the product has Breakthrough Therapy Designation from the FDA. Pfizer and Merck KGaA are studying Entinostat in ovarian cancer in conjunction with Bavencio, their PD-L1 inhibitor monoclonal antibody drug.

- **TapImmune.** This cancer immunotherapy's lead product is TPIV 200, a peptide vaccine originally developed at the Mayo Clinic containing five immunogenic peptide epitopes of the human folate receptor 1. This product is in Phase 2 in ovarian and triple-negative breast cancers[173].

- **Tesaro**. This company, founded in 2010, is notable as having had its start from in-licensing compounds originating in Big Pharma. Tesaro's foundation products were rolapitant, a drug for the treatment of Chemotherapy-Induced Nausea and Vomiting (CINV) originally developed by Schering-Plough, and niraparib, a PARP inhibitor[174] originally developed by Merck & Co. and now being evaluated in ovarian and breast cancer. As Varubi, rolapitant gained FDA approval in September 2015, while as Zejula, niraparib gained FDA approval as an ovarian cancer maintenance therapy in March 2017.
- **Verastem.** This company's lead compound is Duvelisib, a PI3K inhibitor that targets the δ and γ isoforms. We noted above a recently-completed Phase 3 in relapsed or refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. In this study, Duvelisib improved PFS over Novartis' Arzerra drug by 3.4 months, to 13.3 months ($p<0.0001$)[175]. Verastem filed for FDA approval in February 2018. Verastem's defactinib candidate, an inhibitor of the Focal Adhesion Kinase (FAK) pathway, is in Phase 2 in ovarian cancer, in conjunction with Bavencio.

[172] HDAC is an enzyme that helps silence gene expression. The HDAC inhibitors, the first of which was Merck & Co.'s Zolinza (vorinostat), FDA approved in 2006, treat cancer by renewing expression of genes related to cell cycle, apoptosis, and angiogenesis. See Adv Exp Med Biol. 2008;615:261-98.
[173] J Clin Oncol. 2006 Sep 10;24(26):4254-61. Epub 2006 Aug 14.
[174] PARP stands for Poly (ADP-ribose) Polymerase. The PARPs are a family of enzymes which play a role in DNA repair. Other than Tesaro's drug, the approved PARP inhibitors are AstraZeneca's Lynparza (olaparib), FDA approved in December 2014, and Rubraca (generic name rucaparib, see www.rubraca.com), FDA approved in December 2016 for an emerging company called Clovis Oncology (Boulder, Co., Nasdaq: CLVS, www.clovisoncology.com).
[175] See the Verastem press release dated 6 September 2017 and headlined '*Verastem announces positive top-line data from the pivotal Phase 3 DUO study in relapsed or refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma'.*

Table 3: Companies developing glioblastoma therapies

Company	Location	Code	Market cap (USDm)	Web
GW Pharmaceuticals	London, UK	Nasdaq: GWPH	2,990	www.gwpharm.com
NovoCure	St Helier, UK	Nasdaq: NVCR	1,830	www.novocure.com
ZIOPHARM Oncology	New York, NY	Nasdaq: ZIOP	543	www.ziopharm.com
Agenus	Lexington, Ma.	Nasdaq: AGEN	468	www.agenusbio.com
Inovio Pharmaceuticals	Plymouth Meeting, Pa.	Nasdaq: INO	400	www.inovio.com
Mustang Bio	New York, NY	Nasdaq: MBIO	286	www.mustang.com
Tocagen	San Diego, Ca.	Nasdaq: TOCA	226	www.tocagen.com
VBI Vaccines	Cambridge, Ma.	Nasdaq: VBIV	141	www.vbivaccines.com
Northwest Biotherapeutics	Bethesda, Md	Nasdaq: NWBO	116	www.nwbio.com
Vascular Biogenics	Tel Aviv, Israel	Nasdaq: VBLT	66	www.vblrx.com
Moleculin Biotech	Houston, Tx.	Nasdaq: MBRX	47	www.moleculin.com
TRACON Pharmaceuticals	San Diego, Ca.	Nasdaq: TCON	45	www.traconpharma.com
Diffusion Pharmaceuticals	Charlottesville, Va	OTCBB: DFFN	27	www.diffusionpharma.com
Midatech Pharma	Abingdon, UK	LSE: MTPH	23	www.midatechpharma.com
Delmar Pharmaceuticals	Vancouver, BC	OTCQB: DMPI	20	www.delmarpharma.com

Table 4: Companies developing ovarian cancer therapies

Company	Location	Code	Market cap (USDm)	Web
Array Biopharma	Boulder, Co.	Nasdaq: ARRY	3,170	www.arraybiopharma.com
Tesaro	Waltham, Ma.	Nasdaq: TSRO	3,030	www.tesarobio.com
Iovance Biotherapeutics	San Carlos, Ca.	Nasdaq: IOVA	1,400	www.iovance.com
ImmunoGen	Waltham, Ma.	Nasdaq: IMGN	1,350	www.immunogen.com
Adaptimmune Therapeutics	Abingdon, UK	Nasdaq: ADAP	1,040	www.adaptimmune.com
NuCana plc	Edinburgh, UK	Nasdaq: NCNA	642	www.zynerba.com
Syndax Pharmaceuticals	Waltham, Ma.	Nasdaq: SNDX	347	www.syndax.com
Immunovaccine	Halifax, NS	TSX: IMV	207	www.imvaccine.com
Verastem	Cambridge, Ma.	Nasdaq: VSTM	146	www.verastem.com
OncoMed Pharmaceuticals	Redwood City, Ca.	Nasdaq: OMED	120	www.oncomed.com
Celsion	Lawrenceville, NJ	Nasdaq: CLSN	38	www.celsion.com
TapImmune	Seattle, Wa.	Nasdaq: TPIV	36	www.tapimmune.com

Risks related to Kazia Therapeutics

Risks specific to Kazia Therapeutics. We see five major risks for Kazia Therapeutics as a company and as a listed stock:

- **Clinical risk**. There is the risk that Kazia's compounds may fail to meet their primary of secondary endpoints in the clinical trials into which they are taken
- **Funding risk**. More capital will likely be needed to continue clinical development of Kazia's compounds.
- **Drug class risk**. There is the risk that other PI3K inhibitors may make it to market faster than GDC-0084, thereby relegating the drug to a secondary place in the class. The same risk applies to Kazia's other compounds.
- **Timing risk.** There is the risk that the clinical studies we discuss in this note may take longer than we expect to complete.
- **Regulatory risk.** There is the risk that regulatory decisions may slow or stop the progress of Kazia's various products.

Risks related to pre-revenue Life Science companies in general

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Kazia Therapeutics.

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